Age- and Hypertension-Associated Protein Aggregates in Mouse Heart Have Similar Proteomic Profiles

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Abstract—Neurodegenerative diseases are largely defined by protein aggregates in affected tissues. Aggregates contain some shared components as well as proteins thought to be specific for each disease. Aggregation has not previously been reported in the normal, aging heart or the hypertensive heart. Detergent-insoluble protein aggregates were isolated from mouse heart and characterized on 2-dimensional gels. Their levels increased markedly and significantly with aging and after sustained angiotensin II–induced hypertension. Of the aggregate components identified by high-resolution proteomics, half changed in abundance with age (392/787) or with sustained hypertension (459/824), whereas 30% (273/901) changed concordantly in both, each P<0.05. One fifth of these proteins were previously associated with age-progressive neurodegenerative or cardiovascular diseases, or both (eg, ApoE, ApoJ, ApoAIV, clusterin, complement C3, and others involved in stress-response and protein-homeostasis pathways). Because fibrosis is a characteristic of both aged and hypertensive hearts, we poited that aging of fibroblasts may contribute to the aggregates observed in cardiac tissue. Indeed, as cardiac myofibroblasts "sensed" (approached their replicative limit) in vitro, they accrued aggregates with many of the same constituent proteins observed in vivo during natural aging or sustained hypertension. In summary, we have shown for the first time that compact (detergent-insoluble) protein aggregates accumulate during natural aging, chronic hypertension, and in vitro myofibroblast senescence, sharing many common proteins. Thus, aggregates that arise from disparate causes (aging, hypertension, and replicative senescence) may have common underlying mechanisms of accrual. (Hypertension. 2016;67:1006-1013. DOI: 10.1161/HYPERTENSIONAHA.115.06849.) ● Online Data Supplement

Key Words: aging (cardiac) cardiovascular diseases hypertension neurodegenerative diseases protein aggregates

Deaths from atherosclerotic cardiovascular disease (CVD) comprise 31% of all mortality worldwide. Age and hypertension are the major risk factors for atherosclerotic CVD, and both are associated with increased stiffness of the heart. This rigidity, resulting in diastolic dysfunction, is largely attributed to myofibroblast growth and collagen deposition between cardiomyocytes. Knowledge of the mechanisms that contribute to cardiovascular aging would have profound clinical implication for CVD prevention, early detection, and development of therapies.

Most proteins adopt, either spontaneously or with the help of other proteins, specific folded structures with limited degrees of freedom. Chemically altered or misfolded structures, when they occur, are vulnerable to aggregation with other unstructured proteins. Although protein damage and misfolding are inevitable, multiple proteostasis systems are devoted to the repair or clearance of damaged proteins. The heart, in particular, is subject to continuous mechanical and metabolic stress; as a result, the cardiac proteome may be especially reliant on multi-level quality control to ensure proper folding and integrity of proteins. In diverse neurodegenerative disorders, insoluble protein aggregates accrue in neuronal cytoplasm or nuclei, which are thought to comprise misfolded proteins that were not cleared by chaperone-mediated refolding, the ubiquitin-proteasome pathway, or autophagy. Genetic disruption of these pathways can also lead to heritable cardiomyopathies that feature aggregate foci. Although protein aggregation has been studied extensively in neurodegenerative diseases, aggregates that form during normal cardiac aging or sporadic CVD have not previously been characterized.

Aging is accompanied by a state of chronic inflammation termed inflammaging, which is also characteristic of many age-associated diseases such as atherosclerosis, neurodegenerative diseases, and hypertension. Both cardiac aging and sustained hypertension feature elevated levels of reactive oxygen species, which have been implicated in CVD, chronic inflammation, and reduced biosynthesis and availability of nitric oxide.

The ubiquitin-proteasome system is the first line of defense for clearing misfolded and aggregated proteins from...
many tissues, including heart muscle. Despite extensive research on protein aggregation as a mediator of age-dependent functional decline, consideration of its possible role in atherosclerotic CVD has emerged only recently.

In this study, we isolated and quantified compact aggregates from the hearts of young-adult and aged mice and identified their protein constituents. To ask whether the hypertensive state itself disrupts proteostasis and thus mimics aging, we compared protein aggregates from hearts of young mice that were either hypertensive or normotensive. We also examined protein aggregation in early- and late-passage cardiac myofibroblasts, to assess whether their proteostasis is impaired during in vitro senescence and thus may contribute to cardiac senescence in vivo. Protein components of these aggregates were identified and quantified by high-resolution mass spectrometry, revealing a remarkable overlap in constituent proteins among aggregates formed during normal aging and angiotensin II (Ang II)–induced hypertension and (to a lesser extent) in myofibroblast replicative senescence.

**Methods**

We analyzed protein aggregates from young, aged, hypertensive hearts, and fibroblasts isolated from mouse hearts by standard methods. Detailed Material and Methods are available in the online-only Data Supplement.

**Results**

**Cardiac Protein Aggregates Increase in Abundance and Complexity With Age**

Proteins were recovered and solubilized from cardiac-tissue aggregates and resolved on 2-dimensional (2D) gels (isoelectric focusing followed by SDS-PAGE). Results of representative experiments are shown in Figure 1A and 1B. Heart tissue from aged mice (30 months, Figure 1B) showed a dramatic increase in the number and abundance of aggregated protein components, relative to those from young-adult mice (12 months, Figure 1A). Combining data from 3 independent comparisons (Figure 1C), hearts of older mice contained 4.5-fold more aggregated proteins than hearts from young-adult mice ($P=0.01$ by 2-tailed $t$ test; each $n=3$).

**Hypertension Increases the Quantity and Diversity of Aggregated Cardiac Proteins**

Chronic hypertension mimics and accelerates many of the clinical indices of cardiac aging. Because Ang II infusion induces hypertension and initiates cardiac remodeling (cardiomyocyte hypertrophy and extensive fibrosis), and hypertensive hearts show functional declines similar to those observed in naturally aged hearts (eg, loss of compliance), we asked whether mouse hearts exposed to sustained hypertension...
might also show protein aggregates resembling those of aged hearts. Indeed, cardiac tissues of Ang II–infused mice showed a marked elevation in aggregated proteins relative to control (saline-treated) mice of the same age (Figure 1D and 1E). This increase averaged 3.2-fold for 3 independent comparisons (P<0.01 by 2-tailed t test; Figure 1F). The patterns of aggregated proteins observed in 2D gels also became more complex and diverse after Ang II infusion relative to control hearts, but were not as complex as those of cardiac tissue from 30-month-old mice. Although it is not possible to correlate specific protein spots between these 2D profiles, the results suggest that young hypertensive hearts may contain a subset of the aggregate components that appear with normal aging.

**Protein Aggregation Accompanies Replicative Aging of Cardiac Myofibroblasts**

Fibroblasts play important roles in maintaining cardiac structure and function, and predominate during cardiac remodeling that occurs with aging and pressure-overload situations such as sustained hypertension.21 We isolated fibroblasts from hearts of young mice (2.5 months) and propagated them in vitro for 15 mean population doublings, by which time their interdivision time had increased 2.5-fold, indicating replicative senescence. We isolated protein aggregates from myofibroblasts at 3 and 15 mean population doublings and separated their detergent-insoluble fractions from less compact or less stable protein complexes.1 Protein intensity and complexity increased substantially as cells approached their replicative limit. Representative examples of aggregated proteins from cardiac myofibroblasts are shown in Figure 1G and 1H. Although the 2D protein patterns for cardiac myofibroblasts are rather different from those of heart tissue (Figure 1A, 1B, 1D, and 1E), both the pattern complexity and abundance (intensity) of aggregated proteins increased with myofibroblast senescence, paralleling the changes observed in aged and hypertensive hearts. The mean increase (for 2 replicate cultures per group, expanded independently) in aggregate protein content with in vitro senescence was >2-fold (Figure 1; P=0.01 by 2-tailed t test).

**Identification of Aggregated Proteins From Hearts of Normal Young, Aged, or Hypertensive Mice**

Sarcosyl-insoluble protein aggregates isolated from mouse hearts (2 per group) and cultured cardiac myofibroblasts (2 cultures per group) were dissolved by heating in Laemmli buffer, containing a strong ionic detergent (sodium dodecyl sulfate) and a strong reducing agent (β-mercaptoethanol). Constituent proteins of aggregates were then electrophoresed on denaturing polyacrylamide gels, digested with trypsin in excised gel slices, and peptides identified by high-resolution tandem mass spectrometry coupled to nanoflow liquid chromatography. Proteins with Mascot scores >90 (indicating >95% likelihood of correct identification) were considered to be present, and relative quantities of those proteins were estimated from spectral counts (peptide hits) summed for all peptides of each protein. This provides a crude measure of relative protein abundance, uncorrected for protein size (which affects hit frequency but can be neglected when comparing samples for abundance of the same protein).

As mice aged from 3.5 to 30 months, 155 proteins became more abundant, whereas 237 proteins became less abundant in aggregates isolated from cardiac tissue (considering only changes that were significant at P<0.05; Figure 2), far more than would be expected by chance in a total of 787 proteins identified. Hypertension led to similar shifts in the composition of cardiac aggregates, with 223 proteins increasing in abundance and 236 declining, relative to normotensive mice (of 824 identified proteins). Among proteins that increased their abundance in aged hearts, 44% also increased in hearts from mice with sustained hypertension (considering only changes significant at P<0.05; Figure 2). Moreover, 56% of proteins that diminished in aged hearts were also significantly reduced in hypertensive hearts. Conversely, 34% of proteins that became more abundant with hypertension also increased in aged hearts, whereas 61% of proteins that declined in hypertensive hearts also fell in aged hearts. Thus, there was substantial overlap between the shifts in the protein composition of aggregates accompanying aging and hypertension.

Although proteomics indicates more aggregate proteins decreasing than increasing with age (and nearly equal numbers with hypertension), there is no disagreement with the net declines consistently seen in 2D gel analyses (Figure 1). Aggregates were initially scarce in hearts of young, untreated mice (Figure 1A and 1D), so the marked increases that accompany aging and Ang II treatment were far more conspicuous than the declines.

**Selection of Proteins for Validation**

Six of the proteins identified in the aggregate proteomes of heart tissue (heat shock protein 90 [HSP90], fibronectin, cytochrome C, 14-3-3, ApoE, and clusterin) were assessed...
by Western blotting of fresh aggregates isolated from young, aged, and hypertensive mouse hearts. As shown in Figure 3, the levels of these proteins indicated by immunodetection altered with age and hypertension, fully corroborating the proteomics data (indicated by hit counts superimposed over the histogram bars).

Identification of Aggregated Proteins From Cardiac Myofibroblasts Aging In Vitro

A rather different picture emerged from the analysis of proteins in aggregates isolated from cultured cardiac myofibroblasts: 389 proteins increased in abundance with replicative senescence, whereas 166 declined. Overlaps among the aggregated proteins that displayed differential abundance in each comparison are shown as Venn diagrams (Figure 2). The proteins that declined in senescent myofibroblasts were also likely to have decreased in aged hearts (58–60%), whereas proteins that rose in abundance coincided less frequently (15–18%).

Overlapping Profiles of Aggregate Proteins That Change in Abundance With Aging, Hypertension, or In Vitro Senescence

Many of the proteins from sarcosyl-insoluble aggregates, identified by proteomics with high confidence (false discovery rate \( q < 0.05 \)) also shifted in abundance during aging or sustained hypertension or both (considering only changes significant at \( P < 0.05 \); Figure 2). The overlap of these sets was highly enriched for proteins previously shown to play roles in CVD or Alzheimer disease; these are listed in Table S1 in the online-only Data Supplement along with their known functions and spectral counts. Abundance ratios for all proteins found in sarcosyl-insoluble aggregates, contrasting young-adult versus aged, or normotensive versus hypertensive hearts, or cultured cardiac myofibroblasts at 3 or 15 population doublings are shown in Table S2. Of 1393 total proteins identified with confidence (\( q < 0.05 \)) in any sample, 836 were enriched in at least one comparison (2267 significant changes, summed for 3 comparisons), whereas <70 per contrast (<210 for all 3) would be expected to differ by chance at \( P < 0.05 \). A substantial fraction of the proteins that accrued in aggregates from aged and hypertensive hearts had been previously implicated in atherosclerotic CVD (12.1%) or neurodegenerative diseases (6.2%) or both,\(^2\) or other age-dependent diseases (2.1%), for a total of 20.4% (citations in Table S1).

Proteins that were highly abundant in the aged heart, but rare or undetected in hypertension and senescent myofibroblasts, include ApoE, clusterin/ApoJ, complement C3, histones H1t, H2A, and H2B, peristin, vitronectin, and von Willebrand factor A protein. Among these, ApoE, clusterin, and C3 have been implicated in both CVD and Alzheimer disease\(^2\) (citations in Table S1).

Of particular interest are the 98 proteins that increased in heart aggregates with both natural aging and sustained hypertension; these include ApoA-IV, atrial natriuretic factor, cardiac phospholamban, filamin’s A–C, lamin-A/C, myosin-binding protein C, myotilin, obscurin, 9 proteasome subunits, serotransferrin, synaptopodin-2-like, tropomyosin \( \alpha \)-4 chain, vinculin, vitronectin, and xin/actin-binding protein 1.

Proteins that declined dramatically with natural aging and sustained hypertension include 14-3-3 \( \xi \) and \( \epsilon \) (3 other

Figure 3. Representative Western blots for heat shock protein (HSP) 90, fibronectin, vimentin, 14-3-3, ApoE, and clusterin from young, aged, and hypertensive mice. Multiple isoforms (eg, for HSP90, 14-3-3, and ApoE) are not distinguished. ImageJ quantitations of each protein (combined from 3 experiments) are indicated by bars ±SEM, and the spectral counts identified by mass spectrometry are indicated by numbers above each bar. For each gel, the lane with maximum intensity was set to 100%. Significance of differences from the highest-intensity lane (by 2-tailed heteroscedastic \( t \) test) is indicated by * \( P \leq 0.05 \) or ** \( P \leq 0.01 \). Molecular weights of proteins are indicated in kilodaltons (HSP90, 90 kDa; Fibronectin, 220 kDa; cytochrome C, 15 kDa; 14-3-3 proteins, 29 kDa; Apo E, 44 kDa; and clusterin, 36 kDa. A indicates aged; HT, hypertensive; and Y, young).
isoforms also declined somewhat), α-actinin 3, annexin A6, cadherin 2, EH-domain protein 2, γ-enolase, HSP75, myosin 1, neurofilament t. chain, sarcalumenin, sarcoplasmic/endoplasmic reticulum calcium ATPase 1, Ser/Thr phosphatase 2A, SET and MYND-domain–containing protein 1, and ubiquitin-like modifier–activating enzyme 1. Two highly abundant proteins, myosin 1 and sarcoplasmic/endoplasmic reticulum calcium ATPase 1, and 5 less-abundant ones (α-actinin-3, annexin A6, EH-domain protein 2, γ-enolase, and HSP75) were identified only in aggregates from young hearts. Many proteins that declined in aggregate abundance with age or hypertension, or both, are involved in stress responses and protein homeostasis, which are thought to be protective; these include sarcoplasmic/endoplasmic reticulum calcium ATPase 1, α-actinin-3, γ enolase, glycogen phosphorylase, and HSPs.

Gene ontology (GO; functional annotation) analysis has been used to identify pathways and processes implicated by transcriptomics and other "omics" analyses, by looking for enrichment of differentially represented molecular species in each category. We applied DAVID (v.6.7, david.abcc.ncifcrf.gov) analysis to proteins that were either over-represented or (separately) under-represented in aged hearts relative to young-adult hearts. The most significantly age-enriched categories (GO terms or pathways) are listed in Table S3, along with the corresponding data for GO/pathway enrichment in hypertensive heart and in vitro–aged myofibroblasts. Protein categories that were significantly enriched in all 3 contrasts, due to increased protein abundance in aggregates (Table S3A) or decreased abundance (Table S3C), or both, include contractile fiber, proteasome complex, non–membrane-bounded organelle, Alzheimer disease, actin binding, methylation, phosphoprotein, UBL conjugation, mitochondrial, transit peptide, acetylation, cytoskeleton, and ATP-binding. Categories significantly enriched with hypertension but not with cardiac aging are also listed in Table S3B and S3D.

**Discussion**

**Aging, Hypertension, and Proteostasis**

Protein misfolding is a phenomenon observed across all taxa, from bacteria to humans. Nearly a third of newly synthesized proteins misfold and fail to refold with the help of chaperones. Under normal conditions, irreversibly misfolded proteins are cleared by proteasomes; however, aging alters rates of synthesis, modification, folding, processing, and degradation of proteins. Deficiencies in protein quality control can lead to accumulation of aggregates, which are thought to underlie the development of diverse neurodegenerative diseases. In these disease states, proteins coalesce into insoluble aggregates that accumulate with age and disease progression. Examples of proteins in disease-associated aggregates include β-amyloid and tau aggregates (Alzheimer disease); α-synuclein, parkin, DJ-1, and PINK-1 (Parkinson disease); huntingtin, ataxins, and other proteins with long polyglutamine tracts (Huntington disease); mutant forms of actinin-4 (renal failure); and superoxide dismutase (amyotrophic lateral sclerosis). Cytotoxicity of these protein aggregates has been attributed to various factors, such as membrane permeabilization, oxidative and endoplasmic reticulum stress, and mitochondrial dysfunction.

Proteasome activity and quality control have also been reported to be impaired in the aged heart. Because aging is a prominent risk factor for both atherosclerotic CVD and neurodegenerative diseases, we asked whether age-dependent protein aggregation might occur in the heart. Indeed, we observed that aggregates do form in mouse heart and accumulate with age (in vivo and in vitro), and likewise with sustained hypertension. We identified many proteins in cardiac aggregates that are components of the ubiquitin-proteasome system and autophagy (Tables S1 and S2), clearance systems for misfolded proteins that undergo functional declines in cardiac aging and disease. Analysis of the protein composition of aggregates revealed ~400 constituent proteins that differ markedly in abundance between young and old mouse hearts, despite the paucity of age-dependent differences in the total cardiac proteome. Proteins that increased with age were on average 5.1-fold (range of 2- to 50-fold) more abundant in hearts from aged mice, and those that decreased in abundance with age declined by ~3-fold (range, 16% to 25-fold). Changes in protein abundance with hypertension were almost as impressive, averaging 4.6-fold for those that increased, and 2-fold for those that decreased. It is noteworthy that roughly half of the proteins that increased (or decreased) in aged hearts were also enriched (or depleted) in hypertensive hearts. These observations strongly suggest that aging and hypertension feature similar disruptions of protein homeostasis. Some of the interesting differential hits and their roles in diverse physiological processes are compiled in Tables S1 to S3.

Previous studies have sought changes with age in the total proteome of cardiac tissues from mice and rats. Significant shifts in abundance were remarkably rare, comprising <0.01% to 3% of the total proteins identified, and these changes were relatively modest in degree, ranging from 1.2- to 2.5-fold. No significant changes were seen in protein turnover, among >800 proteins monitored in hearts of young and aged rodents. In contrast, we found far larger and more frequent changes with age, among proteins isolated from compact (detergent-insoluble) protein aggregates. The striking contrast in outcomes for whole-proteome versus aggregome discovery implies that aging primarily alters the susceptibility of proteins to aggregate, rather than their synthesis, degradation, or steady-state levels. Furthermore, our observation of significant overlap in protein aggregates between hypertensive and aging hearts suggests that hypertension may in some respects be considered to accelerate or mimic cardiac aging. Physiologically, many functional characteristics of the hypertensive heart mirror those seen with cardiac aging, such as fibrosis and impaired diastolic relaxation.

Because fibrosis results from proliferation and collagen synthesis by fibroblasts, we speculated that protein aggregates in senescent fibroblasts might bear some similarity to those in hypertensive and aged hearts. Although there were many differences, a surprisingly large proportion of aggregated proteins that decreased with myofibroblast aging (150 of 166, or 90%) also declined in heart aggregates with aging or hypertension, or both. Because most of these proteins seem likely to play protective roles, we interpret this as evidence that replicative
Implications of Specific Proteins Found to Accumulate in Aggregates

Proteomic analysis of aggregated proteins indicated marked alterations with age or hypertension, or both, in many proteins previously associated with cardiovascular pathology: these comprise the bulk of proteins listed in Table S1. Some of these, and numerous additional proteins (Tables S1–S3), have been implicated in neurodegenerative diseases such as Alzheimer disease; these include specific 14-3-3 proteins and ApoE, clusterin, complement C3, H1 histones, HSP90 α and β, catalase, laminin γ-1, Nicotinamide adenine dinucleotide-ubiquinone oxidoareductase, plasminogen activator inhibitor-1, peripherin, proteasome α subunits, transthyretin, vimentin, and vitamin D–binding protein.

Specific apolipoprotein species have been implicated in multiple age-related diseases including Alzheimer disease, certain cancers, diabetes mellitus, and renal disease.20,38–40 ApoAI predicts CVD risk, whereas ApoAIV has antioxidant and anti-atherogenic properties. ApoE isoforms are valuable biomarkers of susceptibility to atherosclerotic CVD41,42; the ApoE ε4 allele markedly increases (and the ε2 allele decreases) risk of both CVD and Alzheimer disease.43 In this study, ApoA-I and ApoA-IV were enriched in aggregates of hypertensive hearts, whereas ApoE was exclusively abundant in aged heart (164 hits, versus 0 for young and hypertensive [HT] hearts). Clusterin (ApoJ), an extracellular chaperone thought to oppose aggregation of plasma proteins, was similarly abundant in aggregates from old and hypertensive heart, perhaps indicating its induction by nascent aggregates, but was absent from young cardiac aggregates.

Protective/proteostatic HSPs (HSP70, HSP90α, and HSP90β) were significantly depleted in aggregates from aged hearts, whereas HSP75, a mitochondrial HSP that protects against cardiac hypertrophy and fibrosis,44 was absent from both aged and hypertensive heart aggregates (Table S1). Several large HSPs, especially HSP70 and HSP60, are elevated in the offspring of centenarians relative to age-matched controls45 suggesting protective functions. In contrast, the small HSPs (HSP-β6, HSP-β7, and HSP-β8) are more abundant in aged-heart aggregates (Tables S1 and S2). They colocalize with amyloid plaques in neurodegenerative diseases,46,47 suggesting entrapment in aggregates or roles in reducing aggregate toxicity.

Previous reports have indicated that expression in heart declines with rat age for actin, tropomyosin, and troponin—proteins responsible for cardiac contractility.48 We found more tropomyosin in the aggregates of aged and hypertensive hearts, suggesting that increased sequestration of tropomyosin within aggregates may contribute to the decreased contractility of aged and hypertensive hearts. Periostin is also more abundant in heart with both aging and hypertension and in cardiac myofibroblasts with replicative senescence. Periostin is a major transforming growth factor-β target involved in tissue remodeling and angiogenesis after injury49,50; indeed, cardiac healing is impaired in periostin-knockout mice after acute myocardial infarction.49 Genomewide association studies found periostin alleles to be strongly associated with early-onset atherosclerosis.51 Sequestration of periostin in aggregates may contribute to age- and hypertension-impaired healing of cardiac injury.

Of 11 proteasome subunits identified in cardiac aggregates, 9 were enriched (and 2 depleted) with aging, and 10 were enriched with hypertension (Tables S1 and S2). Proteasome activity declines with age and under conditions of high protein aggregation and seems to involve entrapment of proteasomes within aggregates.1 Aggregation of proteasomes would impair protein degradation, consistent with the reported decline in proteasome activity with cardiac aging.32 Complement C3, a marker of inflammation, was elevated 14-fold in aggregates from aged heart. C3 is activated in age-related macular degeneration52–54 and is associated with increased amyloid-plaque deposition.55

Lessons From GO Meta-Analysis

GO analysis of the aggregate proteome can provide insight into specific pathways, processes, and cell structures that contribute to aggregation. By their nature, however, they ignore random events as well as processes that depend on unannotated features of proteins, such as intrinsic disorder, low thermal stability, hydrophobicity, or propensity for disruptive postsynthetic modifications. Meta-analysis of aggregate proteins that increased with age (Table S3A) highlighted categories for extracellular matrix, contractile fiber, nucleosome, protein:DNA complex, and proteasome complex (enriched 19- to 27-fold; each P<2E−9). Intriguingly, Alzheimer disease–related proteins were enriched 7.4-fold (P<2E−8). Among categories of proteins decreasing with age (Table S3B), mitochondrion, acetylation, generation of precursor metabolites, transit peptides, and cell respiration were enriched 5.5- to 37-fold (each P<2E−15). Proteins associated with Parkinson disease (11-fold; P=2E−12) and Huntington disease (8-fold; P=2E−10) were not far behind, suggesting that proteostasis-protection pathways commonly defective in those diseases are also impaired with cardiac aging.

Hypertension as a Caricature of Normal Cardiovascular Aging

GO categories (Table S3), like individual proteins (Tables S1 and S2), underscore the many commonalities in aggregate composition between cardiac aging and hypertension and (to a lesser extent) in vitro aging of cardiac myofibroblasts (Figure 2). The overlap in protein-aggregate composition between hypertensive and aged hearts is especially remarkable, suggesting that hypertension, a known risk factor of CVD, is linked to age-associated CVD risk through protein aggregation. The observation that angiotensin-induced hypertension recapitulated many of the same aggregate characteristics seen in normal aging, but at a young age, implies that hypertension may be the proximal culprit, contributing many causal factors exacerbated by aging. Although we cannot formally exclude the alternative possibility that hypertension itself accelerates cardiac aging, this would be a tenuous hypothesis on purely mechanistic grounds. Furthermore, some age-dependent changes in protein aggregation were also seen during myofibroblast senescence. With both aging and sustained hypertension, fibroblasts proliferate and contribute to fibrosis; this could account for part of the observed overlap in protein-aggregate composition between cardiac aging and
hypertension. Other differences, not explained by myofibroblasts, could be attributed to changes in other cell types, for example, cardiomyocytes and endothelial cells.

Aggregation Links Cardiovascular Aging to Age-Progressive Neuropathies

We were particularly intrigued by similarities in protein-aggregation levels and constituents in aged or hypertensive hearts, to those reported in neurodegenerative diseases (Table S1). It was recently speculated that cardiac aging may be considered as Alzheimer disease of the heart, and our observations may be the strongest evidence to date for this proposition. A further, unforeseen finding is that hypertensive hearts have much in common with 2 other aggregation-defined neurodegenerative diseases, Parkinson disease and Huntington disease (Table S3B). This implies that cardiac aggregation accompanying aging or hypertension reflects a molecular pathology remarkably similar to progressive neurological diseases. The current studies provide, for the first time, a plausible mechanism to explain this puzzling convergence between such disparate but highly age-associated diseases: aggregates form as a concomitant of aging, but produce distinct pathologies in each susceptible tissue.

Clinical Perspectives

Protein damage and misfolding are common features of aging-related neurological disorders like Alzheimer disease and Huntington chorea. These disorders in proteostasis may be the basis of aging in general and may affect the heart as well. Hypertensive and aged hearts show similar dysfunction of the heart, related most likely to the development of fibrosis. This study revealed that indeed there are significant changes in proteostasis in the aged heart as well as in the hypertensive heart. Furthermore, there was a significant overlap in upregulated and downregulated proteins in aged heart and the hypertensive heart. Senescent myofibroblasts in culture also showed a significant overlap in the consequences of impaired proteostasis, with the aged heart and the hypertensive heart. Finally, the aged and hypertensive heart shared some features of the aged heart in neurological disorders. Thus, hypertension seems to be caricature of normal cardiovascular aging, and both conditions may be considered “Alzheimer disease” of the heart.

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Disclosures

None.

References

Novelty and Significance

What Is New?

- There are significant changes in proteostasis in the aged heart and in the hypertensive heart. Both involve the formation of detergent-insoluble aggregates, not previously reported.
- There was a significant overlap of aggregated proteins in aged heart and the hypertensive heart.
- Senescent myofibroblasts in culture showed a lesser but significant overlap in aggregate proteins with those of aged heart and the hypertensive heart.

What Is Relevant?

- Based on this proteomic study, hypertension seems to accelerate or mimic some aspects of normal physiological aging.
- Aggregates formed in the aged heart and the hypertensive heart share some features with the aged brain, in particular features that are markedly increased in neurological disorders.

Summary

Both aging and chronic hypertension lead to the accumulation of similar aggregates in the heart, many of which overlap the aggregates that occur in the cortex of Alzheimer patients.
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Age- and hypertension-associated protein aggregates in mouse heart have similar proteomic profiles

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\textbf{Running Title:} Protein aggregation in aged and hypertensive heart

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Data Supplement

Materials and Methods

Mice

C57BL/6J male mice were maintained under conditions approved by the Institutional Animal Care and Use Committee. Mice (at 3.5 and 30 months of age, 5 per group) were sacrificed by intra-peritoneal injection of pentobarbital (60 mg/kg). Hearts were removed and left ventricular tissue (subsequently referred to as heart tissue) was dissected for aggregate quantitation (3 per group) and aggregate protein characterization (2 per group).

Hypertension was induced by continuous infusion of angiotensin II (Ang II; 50ng/min for 28 days) into C57BL/6J mice beginning at 75 days of age. In a parallel control group, mice were infused with saline. The Ang II-treated group developed sustained elevated blood pressure as described previously (1). Five mice were sacrificed per group (at ~3.5 months of age) under pentobarbital anesthesia followed by collection of left ventricular tissue, utilized for analyses as described above.

Isolation and culture of cardiac fibroblasts

Fibroblasts were isolated from mouse hearts by standard methods (2). Briefly, mice were sacrificed at 10 weeks of age by pentobarbital anesthesia, and their hearts removed and minced in sterile phosphate-buffered saline (PBS) with sterile scissors, then immersed for 30 sec in 70% ethanol to remove endothelial cells. Minced tissue was digested with trypsin (0.25%, w/v, in PBS), for 10 min at 37°C, and the process
repeated 5–6 times. Cells freed from the extracellular matrix were collected after each cycle by brief centrifugation (1000 x g for 6 min), combined, transferred to flasks, and cultured in DMEM supplemented with 5% FBS at 37°C under 5% CO₂. Myofibroblasts were cultured for 15 mean population doublings (MPD), i.e. 15 passages at a 1:2 split ratio, and harvested at passages 3 and 15 (termed “young” and “senescent” respectively) for analyses of protein aggregation.

**Aggregate purification and 2D separation and quantitation of proteins**

Heart tissue from young and aged mice, or from hypertensive and normotensive-control mice, were flash frozen in liquid nitrogen. Tissue samples were pulverized in a dry-ice-cooled mortar, and suspended in lysis buffer (20-mM Hepes pH 7.4, 0.3-M NaCl, 2-mM MgCl₂, 1% NP40 (w/v), and phosphatase/protease inhibitors [CalBiochem]). Cultured cardiac myofibroblasts were lysed in the same buffer. After centrifugation (5 min, 2000 x g) to remove debris, organelles and particulates, the protein concentration was determined (Bradford Protein Assay, Bio-Rad).

Protein samples were centrifuged at 14,000g for 15 minutes and the supernatants removed. Pellets were suspended in 0.1-M HEPES buffer containing 1% sarcosyl (v/v), 5-mM EDTA, and protease inhibitors, followed by 30 min centrifugation at 100,000 x g. Each detergent-insoluble fraction (100,000-g pellet) was suspended in 125 µl IEF loading buffer (8-M urea, 2% CHAPS, 40-mM DTT, 0.2% Biolyte) and resolved by 2-D gel electrophoresis. Proteins were first separated in ampholytes by isoelectric focusing, pH 3–10, then electrophoresed on 1% sodium dodecylsulfate (SDS), 4–12% polyacrylamide gradient gels (Invitrogen), and visualized by staining with SYPRO Ruby.
(Invitrogen). Protein fluorescence intensities were quantitated using ImageJ software (NIH, Bethesda, MD).

Protein identification

Protein components of aggregate fractions were suspended in Laemmli buffer containing 2% SDS (w/v) and 0.5% (v/v) β-mercaptoethanol, and dissolved by heating 5 min at 95°C. Proteins were separated in one dimension on 1% SDS, 4‒12% acrylamide gradient gels, then stained with SYPRO Ruby (Invitrogen) or Coomassie Blue for total protein, and 1-mm slices were excised. Proteins were digested in situ with trypsin, and peptides analyzed by high-resolution LC-MS/MS with a Thermo Velos Orbitrap mass spectrometer coupled to a waters nanoACQUITY LC system as previously reported (3). Proteins were identified by MASCOT (www.matrixscience.com) matching of peptide fragmentation patterns to a database of predicted patterns (3).

Western blotting

Heart tissue, pooled from 3 mice per group, was homogenized and aggregate protein was extracted as described above. Aggregate protein was dissolved by heating to 95°C in Laemmli buffer and electrophoresed on a 4‒12% SDS-acrylamide gel, and transferred to nitrocellulose membrane. The membranes were probed, according to manufacturer’s instructions, with antibodies against rabbit HSP90 (Stressgen, British Columbia, Canada) rabbit cytochrome C (Abcam, Cambridge, MA), mouse 14-3-3 (SantaCruz Biotechnology, Dallas, TX), rabbit ApoE (Thermo Fisher, Grand Island, NY), rabbit clusterin (Santa Cruz Biotechnology), or rabbit fibronectin (Abcam). Anti-mouse IgG or anti-rabbit IgG secondary antibodies conjugated to horseradish peroxidase
(SantaCruz Biotechnology) were used to detect protein by chemiluminiscence (Thermo-Fisher ECL detection kit). Protein bands were quantified using Image J software.

Statistical analysis

Differences between groups were assessed for significance by the Fisher-Behrens heteroscedastic $t$ test (appropriate to samples of unequal or unknown variance). Differences in peptide abundance, based on spectral counts, were assessed for significance by chi-squared tests.

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(51) Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van HF, van Duijn CN, Van BC, Grobbbee DE. Atherosclerosis, apolipoprotein E, and prevalence of


Browman DT, Resek ME, Zajchowski LD, Robbins SM. Erlin-1 and erlin-2 are novel members of the prohibitin family of proteins that define lipid-raft-like domains of the ER. *J Cell Sci.* 2006; 119:3149-3160.


(174) Huang H, Joseph LC, Gurin MI, Thorp EB, Morrow JP. Extracellular signal-regulated kinase activation during cardiac hypertrophy reduces


(207) Chiu DS, Oram JF, LeBoeuf RC, Alpers CE, O'Brien KD. High-density lipoprotein-binding protein (HBP)/vigilin is expressed in human atherosclerotic


(214) Yoo BC, Fountoulakis M, Cairns N, Lubec G. Changes of voltage-dependent anion-selective channel proteins VDAC1 and VDAC2 brain levels in patients


Table S1. Approximately half of the proteins that are differentially abundant in aggregates with cardiac aging or hypertension, are listed here along with their roles in cardiovascular or other age-related diseases, and spectral counts (peptide “hits”) obtained from cardiac aggregates of young (Y), aged (A) and hypertensive (HT) mice.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Role in Cardiovascular Aging and Other Age-Dependent Diseases</th>
<th>Y</th>
<th>A</th>
<th>HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-3-3 proteins*</td>
<td>Signal-transduction roles; interact w. tau; diabetic CVD, Alzheimer-disease risk factors</td>
<td>28</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Alpha-actinin-3</td>
<td>F-actin cross-linking protein, angiotensin-II induced; implicated in chronic heart failure</td>
<td>61</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Annexin A6</td>
<td>Decreased in DMD cardiomyopathy; associated with regulation of Ca^2+ in the heart</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>Risk indicator of coronary heart disease</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Apolipoprotein A-IV</td>
<td>Serum marker of coronary artery disease prognosis</td>
<td>0</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Apolipoprotein E*</td>
<td>Affects lipoprotein metabolism, vasculature; allelic risk factor for CVD and Alzheimer’s</td>
<td>0</td>
<td>164</td>
<td>0</td>
</tr>
<tr>
<td>Atrial natriuretic factor</td>
<td>Alleles are associated with risk of cardiovascular disease</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Cadherin-2</td>
<td>Ca^{++}-dependent cell adhesion protein; altered expression leads to cardiomyopathies</td>
<td>21</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac phospholamban</td>
<td>Key regulator of cardiac contractility, implicated in heart-failure pathology</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Catalase</td>
<td>Antiox. enzyme opposing H_{2}O_{2} toxicity, DNA damage, apoptosis, CHD cardiomyopathy</td>
<td>2</td>
<td>6</td>
<td>1*</td>
</tr>
<tr>
<td>Clusterin*</td>
<td>Chaperone (a.k.a. apolipoprotein J) for plasma-protein aggregation; implic. in CVD, AD</td>
<td>0</td>
<td>50</td>
<td>3*</td>
</tr>
<tr>
<td>Complement C1q, s.u. A</td>
<td>C1q deficiency increases risk of bacterial infections, skin lesions, &amp; autoimmunity (SLE)</td>
<td>0</td>
<td>9</td>
<td>2*</td>
</tr>
<tr>
<td>Complement C3*</td>
<td>Marker of CHD, CVD &amp; Alzheimer risk; associated with serum TAG, atherosclerosis</td>
<td>2</td>
<td>28</td>
<td>3*</td>
</tr>
<tr>
<td>Cytochrome c, somatic</td>
<td>Heme protein of mitochondrial ETC; apoptosis (e.g., due to myocardial ischemia)</td>
<td>4</td>
<td>8*</td>
<td>24</td>
</tr>
<tr>
<td>EH domain protein 2</td>
<td>EH domain proteins regulate cardiac-membrane protein targeting</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatty acid-binding protein</td>
<td>Cardiac form; increased levels are associated with acute coronary events and death</td>
<td>20</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Filibrin-1,-2</td>
<td>Major components of connective tissue microfibrils, Fbn-1 is involved in CV disorders</td>
<td>67</td>
<td>157</td>
<td>60*</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>Serum levels significantly reduced with coronary heart disease, esp. congenital CHD</td>
<td>19</td>
<td>86</td>
<td>22*</td>
</tr>
<tr>
<td>Filamin-A</td>
<td>Filamins interact with integrins, transmembrane receptor complexes, 2nd messengers</td>
<td>7</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Filamin-B</td>
<td>Defects impair cardiac development</td>
<td>0</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Filamin-C</td>
<td>Splicing of filamin C gamma (FLNC) is significantly altered in ischemic cardiomyopathy</td>
<td>53</td>
<td>184</td>
<td>144</td>
</tr>
<tr>
<td>Gamma-enolase</td>
<td>Serum neuron-specific enolase; predicts outcome following cardiac arrest</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glial fibrillary acidic protein</td>
<td>“Brain-specific” marker of congenital heart disease, brain injury during cardiac surgery</td>
<td>12</td>
<td>0</td>
<td>8*</td>
</tr>
<tr>
<td>Glycogen phosphorylase</td>
<td>Brain form; sensitive &amp; specific indicator of ischemic tissue damage in heart failure</td>
<td>18</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>GST A2</td>
<td>Protective GSTs, with glutathione peroxidase activity; marker of CHD, oxidative stress</td>
<td>0</td>
<td>4</td>
<td>1*</td>
</tr>
<tr>
<td>Histone H1.4</td>
<td>Inter-nucleosome histone; condenses chromatin; binds amyloid fibrils in Alzheimer’s</td>
<td>23</td>
<td>53</td>
<td>21*</td>
</tr>
<tr>
<td>Histone H1t</td>
<td>Inter-nucleosome histone; condenses chromatin; binds amyloid fibrils in Alzheimer’s</td>
<td>0</td>
<td>16</td>
<td>0*</td>
</tr>
<tr>
<td>Histone H2A type 2-B</td>
<td>Core component of nucleosome; epigenetic regulator of expression; implicated in HD</td>
<td>0</td>
<td>8</td>
<td>0*</td>
</tr>
<tr>
<td>Histone H2B type 2E</td>
<td>Core component of nucleosome, involved in epigenetic regulation of expression</td>
<td>0</td>
<td>45</td>
<td>0*</td>
</tr>
<tr>
<td>HSP 90-α</td>
<td>Chaperone for protein folding, quality control; implicated in tau &amp; prion aggregation</td>
<td>23</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>HSP 90-β</td>
<td>Chaperone for protein folding, quality control; implicated in tau &amp; prion aggregation</td>
<td>32</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>HSP75, mitochondrial</td>
<td>Chaperone implicated in aging, proteostasis; protects against ischemia in rat brain</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Junctophilin-2</td>
<td>Silencing results in cardiomyocyte hypertrophy, abnormal calcium-flux</td>
<td>19</td>
<td>0</td>
<td>24*</td>
</tr>
<tr>
<td>Lamin-A/C</td>
<td>Nuclear envelope prot.; mutations implicated in dilated cardiomyopathy, HG progeria</td>
<td>44</td>
<td>105</td>
<td>75</td>
</tr>
<tr>
<td>Laminin subunit α-2, 4, 5</td>
<td>ECM glycoprotein involved in cell adhesion; implic. in cardiac myopathy, hypertrophy</td>
<td>281</td>
<td>567</td>
<td>179</td>
</tr>
<tr>
<td>Laminin subunit β-1, 2</td>
<td>β-2 deficiency implic. in cardiomyopathy (aged mdx model of Duchenne musc. dys.)</td>
<td>282</td>
<td>505</td>
<td>208*</td>
</tr>
<tr>
<td>Laminin subunit-1</td>
<td>Deficient in astrocytes (grey and white matter) of AD brain compared to normal brain</td>
<td>164</td>
<td>280</td>
<td>156*</td>
</tr>
<tr>
<td>Leucine-rich PPR motif-containing protein</td>
<td>Plays role in cytoskeletal organization, vesicular transport, &amp; transcriptional regulation of nuclear &amp; mitochondrial genes; implicated in gastric cancer</td>
<td>21</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Lipoprotein lipase</td>
<td>Involved in lipid metabolism disorders; risk factor for ischemic stroke and CHD</td>
<td>6</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Low-MW phospho-Tyr protein phosphatase</td>
<td>Acts on tyr-phosphoproteins, low-MW aryl phosphates and acyl phosphates. Low levels contribute to development of diabetes.</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Myosin-1</td>
<td>Muscle contractile protein, altered in cardiac hypertrophy</td>
<td>804</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myosin-binding prot. C</td>
<td>Cardiac form, protects vs. cardiomyopathy; phosphorylation alters cardiac contraction</td>
<td>263</td>
<td>373</td>
<td>542</td>
</tr>
<tr>
<td>Myotilin</td>
<td>Stabilizes thin filament during cardiac contraction; implicated in myofibrillar myopathy</td>
<td>0</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>Na+/K+ ATPase s.u. α-2</td>
<td>Knockout results in cardiomyopathy</td>
<td>62</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>NADH deHase [ubiquinone] Fe/S proteins 5 &amp; 6</td>
<td>Biomarkers of Alzheimer’s, Down syndrome, and possibly of ischemic heart damage</td>
<td>6</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>Protein</td>
<td>Description</td>
<td>A (Aged)</td>
<td>HT (Hypertensive)</td>
<td>Y (Young)</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>NADH-ubiquinone oxidoreductase chain 5</td>
<td>Reduced in brains of Down syndrome and Alzheimer, Huntington patients</td>
<td>0</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Neurofilament L chain</td>
<td>CSF biomarker for ALS and Alzheimer’s; also expressed in early-stage breast cancer</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nidogen-1</td>
<td>Decreased in cardiomyopathy (‘aged mdx’ model of Duchenne muscular dystrophy)</td>
<td>116</td>
<td>248</td>
<td>110†</td>
</tr>
<tr>
<td>Obscurin</td>
<td>Role in myofibrillar cluster assembly; implic. in cardiac myofibrillogenesis, hypertrophy</td>
<td>35</td>
<td>68</td>
<td>72</td>
</tr>
<tr>
<td>Periostin</td>
<td>Implic. in cardiac remodeling; used as an injectable therapeutic agent for heart failure</td>
<td>0</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Peripherin</td>
<td>Mutations are associated with amyotrophic lateral sclerosis (ALS), neuronal death</td>
<td>6</td>
<td>0</td>
<td>5†</td>
</tr>
<tr>
<td>Peroxiredoxin-6*</td>
<td>Implicated in Parkinson’s; disruption raises risk of cardiac ischemia-reperfusion injury</td>
<td>0</td>
<td>1†</td>
<td>9</td>
</tr>
<tr>
<td>Plasminogen activ.inh.1</td>
<td>PAI-1 deficiency raises bleeding risk in trauma, surgery; implicated in Alzheimer’s</td>
<td>0</td>
<td>3†</td>
<td>4</td>
</tr>
<tr>
<td>Plectin-1</td>
<td>Cytoskeletal linker protein, important in neuromuscular synapse integrity</td>
<td>69</td>
<td>109</td>
<td>42†</td>
</tr>
<tr>
<td>Proteasome s.u. α-5, 6, 7</td>
<td>Catalytic subunits; implic. in tau, synuclein pathologies (e.g. Alzheimer’s, Parkinson’s)</td>
<td>2</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Proteasome s.u. β-2, 4, 8</td>
<td>Regulatory subunits; β-8 responds to γ-interferon, implicated in auto-inflammation</td>
<td>4</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Sarcalumenin</td>
<td>Maintains cardiac function during aging, endurance exercise training</td>
<td>49</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Sarco-/endoplasmic reticulum Ca** ATPase 1</td>
<td>Plays a major role in controlling excitation/contraction coupling; implicated in CVD</td>
<td>133</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ser/thr-phosphatase 2A 65 kDa reg. s.u. A-α</td>
<td>Scaffolding protein, coordinates assembly of phosphatase catalytic &amp; regulatory subunits; implicated in Alzheimer and Parkinson tauopathies</td>
<td>22</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serotransferrin</td>
<td>Biomarker decreased in rheumatic valvular heart disease</td>
<td>16</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>SET and MYND domain-containing protein 1</td>
<td>Methy1ates histone H3 (H3K4me) in cardiomyocyte differentiation &amp; cardiac morphogenesis; implicated in cancer and cardiac dysfunction</td>
<td>15</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>SOD [Mn], mitochondrial Stress-70 protein, mitoc.</td>
<td>Implicated in diabetic CHD, rheumatic heart disease</td>
<td>7</td>
<td>7†</td>
<td>16</td>
</tr>
<tr>
<td>Synaptotropin 2-like</td>
<td>Cytoskeletal Heart-enriched Actin-assoc. Protein (CHAP) increased in striated muscle</td>
<td>2</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>Transthyretin*</td>
<td>Alzheimer cofactor; mutations affect amyloid deposits in heart and peripheral nerves</td>
<td>0</td>
<td>2†</td>
<td>6</td>
</tr>
<tr>
<td>Tropomyosin α-4 chain</td>
<td>Binds actin filaments; helps regulate striated muscle contraction; implicated in breast ca.</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Ubiquitin-like modifier-activating enzyme 1</td>
<td>Catalyzes ubiquitin conjugation of proteins to be degraded; implicated in Alzheimer’s</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vimentin*</td>
<td>Binds regulates ALOX15 promoter; implicated in dilated cardiomyopathy, Alzheimer’s</td>
<td>138</td>
<td>213</td>
<td>126†</td>
</tr>
<tr>
<td>Vinculin</td>
<td>Decreased expression, mutations associated w. myocardial ischemia, atherosclerosis</td>
<td>7</td>
<td>28</td>
<td>49</td>
</tr>
<tr>
<td>Vitamin D binding prot.*</td>
<td>Activates macrophages; suppresses plaque in Alzheimer disease; implicated in CAD</td>
<td>1</td>
<td>4†</td>
<td>9</td>
</tr>
<tr>
<td>Vitronectin</td>
<td>Protein associated with CVD; also predicts risk for patients receiving coronary stents</td>
<td>6</td>
<td>81</td>
<td>14</td>
</tr>
<tr>
<td>vWF A protein 1</td>
<td>Von Willebrand factors aid in matrix assembly, favor platelet adhesion; implicated in CVD</td>
<td>0</td>
<td>21</td>
<td>3†</td>
</tr>
<tr>
<td>Xin (actin-BP 1)</td>
<td>Striated muscle-specific F-actin binding protein, implicated in skeletal, cardio-myopathies</td>
<td>1</td>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>

*Proteins implicated in both cardiovascular and neurodegenerative diseases; see Supplementary Table S1 for references.

†Spectral counts for these aggregate proteins from aged (A) or hypertensive (HT) mice did not differ with at least nominal significance (chi-squared P<0.05) from those for young-normal controls (Y).

All other A and HT counts met that criterion.
Table S2. Full list of proteins identified in aggregates that were differentially represented with aging, hypertension, or myofibroblast replicative senescence.

<table>
<thead>
<tr>
<th>Identified Proteins [implicated in CVD and other age-related diseases]</th>
<th>Aged/Young</th>
<th>HT/Control</th>
<th>P15/P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-kDa heat shock protein, mitoch. [diabetes, autoimmunity(4)]</td>
<td>—</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>116-kDa U5 small nuclear ribonucleoprotein component</td>
<td>—</td>
<td>—</td>
<td>2.1</td>
</tr>
<tr>
<td>14-3-3 protein beta/alpha [diabetic cardiomyopathy(5)]</td>
<td>0.67</td>
<td>0.33</td>
<td>1.1</td>
</tr>
<tr>
<td>14-3-3 protein epsilon [neurological disorders(6)]</td>
<td>0.25</td>
<td>0.875</td>
<td>1.0</td>
</tr>
<tr>
<td>14-3-3 protein gamma</td>
<td>0.5</td>
<td>0.13</td>
<td>1.1</td>
</tr>
<tr>
<td>14-3-3 protein theta</td>
<td>0.75</td>
<td>only in NT</td>
<td>1.5</td>
</tr>
<tr>
<td>14-3-3 protein zeta/delta</td>
<td>0.36</td>
<td>0.18</td>
<td>1.0</td>
</tr>
<tr>
<td>26S protease regulatory subunit 6A [heart disease(7-9)]</td>
<td>only in young</td>
<td>only in NT</td>
<td>2.0</td>
</tr>
<tr>
<td>26S protease regulatory subunit 7 [neuroinflammation(10)]</td>
<td>only in young</td>
<td>only in NT</td>
<td>0.60</td>
</tr>
<tr>
<td>26S proteasome non-ATPase regulatory subunit 1 [macular degeneration(11)]</td>
<td>only in young</td>
<td>only in HT</td>
<td>2.2</td>
</tr>
<tr>
<td>28S ribosomal S21, mitoch.</td>
<td>only in young</td>
<td>only in NT</td>
<td>only in P15</td>
</tr>
<tr>
<td>2-oxoglutarate dehydrogenase, mitoch. [neurodegeneration(12)]</td>
<td>0.24</td>
<td>0.69</td>
<td>5.0</td>
</tr>
<tr>
<td>3,2-trans-enoyl-CoA isomerase, mitoch.</td>
<td>0.11</td>
<td>0.22</td>
<td>only in P15</td>
</tr>
<tr>
<td>39S ribosomal protein L28, mitoch.</td>
<td>only in young</td>
<td>only in NT</td>
<td>only in P15</td>
</tr>
<tr>
<td>3-hydroxyacyl-CoA dehydrogenase type-2 [cardiac mitochondrial(13)]</td>
<td>only in young</td>
<td>1.3</td>
<td>1.3</td>
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<tr>
<td>3-hydroxyisobutyryl-CoA hydrolase, mitoch. [neurodegeneration(14)]</td>
<td>only in young</td>
<td>0.60</td>
<td>only in P15</td>
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<tr>
<td>3-ketoacyl-CoA thiolase A, peroxisomal</td>
<td>only in young</td>
<td>only in NT</td>
<td>only in P15</td>
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<tr>
<td>3-ketoacyl-CoA thiolase, mitoch. [angina(15)]</td>
<td>0.39</td>
<td>0.59</td>
<td>0.75</td>
</tr>
<tr>
<td>40S ribosomal protein S11</td>
<td>0.55</td>
<td>0.36</td>
<td>0.58</td>
</tr>
<tr>
<td>40S ribosomal protein S12</td>
<td>0.50</td>
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<td>1.0</td>
</tr>
<tr>
<td>40S ribosomal protein S13</td>
<td>0.17</td>
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</tr>
<tr>
<td>40S ribosomal protein S14</td>
<td>0.81</td>
<td>0.18</td>
<td>0.78</td>
</tr>
<tr>
<td>40S ribosomal protein S15a</td>
<td>2.2</td>
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<td>40S ribosomal protein S16</td>
<td>0.67</td>
<td>0.27</td>
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<tr>
<td>40S ribosomal protein S17</td>
<td>—</td>
<td>only in HT</td>
<td>4.5</td>
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<tr>
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<td>0.50</td>
<td>0.68</td>
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<td>1.0</td>
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<td>only in young</td>
<td>only in NT</td>
<td>0.59</td>
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<td>only in NT</td>
<td>0.36</td>
</tr>
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<td>4.0</td>
<td>0.67</td>
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<tr>
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<td>only in aged</td>
<td>only in HT</td>
<td>1.8</td>
</tr>
<tr>
<td>40S ribosomal protein S6</td>
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<td>0.85</td>
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<td>40S ribosomal protein S7</td>
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<td>1.3</td>
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<td>1.2</td>
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<td>40S ribosomal protein S9</td>
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<td>7.0</td>
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<tr>
<td>40S ribosomal protein SA</td>
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<td>0.82</td>
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<tr>
<td>6.8 kDa mitoch. proteolipid</td>
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<td>0.63</td>
<td>only in P15</td>
</tr>
<tr>
<td>Protein Name</td>
<td>Fold Change</td>
<td>Location</td>
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</tr>
<tr>
<td>--------------------------------------------------</td>
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<td>60 kDa heat shock protein, mitoch. [cardiovascular disease; pathogens(16-18)]</td>
<td>0.05</td>
<td>0.27</td>
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<tr>
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<td>only in HT 2.0</td>
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<tr>
<td>60S acidic ribosomal protein P2</td>
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<tr>
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<td>5.0</td>
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<td>only in aged</td>
<td>only in HT 0.92</td>
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<td>60S ribosomal protein L15</td>
<td>—</td>
<td>only in HT 0.63</td>
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<tr>
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<td>only in aged</td>
<td>only in HT 1.8</td>
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<td>only in aged</td>
<td>only in HT 0.73</td>
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<td>only in aged</td>
<td>only in HT 1.8</td>
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<td>0.67</td>
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<td>0.29</td>
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<td>1.4</td>
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<tr>
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<td>0.80</td>
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<td>1.4</td>
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<td>60S ribosomal protein L34</td>
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<td>60S ribosomal protein L5</td>
<td>only in aged</td>
<td>only in HT 1.7</td>
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<td>3.6</td>
<td>1.3</td>
</tr>
<tr>
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<td>only in young</td>
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<td>0.85</td>
</tr>
<tr>
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<td>1.3</td>
</tr>
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<td>5.0</td>
<td>0.52</td>
</tr>
<tr>
<td>60S ribosomal protein L9</td>
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<td>1.0</td>
<td>1.3</td>
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<tr>
<td>6-phosphofructokinase, muscle type</td>
<td>0.06</td>
<td>0.11</td>
<td>only in P15</td>
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<tr>
<td>Acetyl-CoA acetyltransferase, mitoch. [neurodegeneration(19)]</td>
<td>0.07</td>
<td>0.19</td>
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<tr>
<td>Acetyl-coenzyme A synthetase 2-like, mitoch.</td>
<td>0.22</td>
<td>0.56</td>
<td>only in P15</td>
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<tr>
<td>Aconitate hydratase, mitoch. [dilated cardiomyopathy (20)]</td>
<td>0.27</td>
<td>0.47</td>
<td>1.0</td>
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<tr>
<td>Actin-related protein 2/3 complex subunit 1B</td>
<td>—</td>
<td>only in HT 6.3</td>
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</tr>
<tr>
<td>Actin-related protein 2/3 complex subunit 2</td>
<td>—</td>
<td>only in HT 8.5</td>
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</tr>
<tr>
<td>Actin-related protein 2/3 complex subunit 4</td>
<td>only in aged</td>
<td>only in HT 1.8</td>
<td></td>
</tr>
<tr>
<td>Protein/Marker Description</td>
<td>Only in Young</td>
<td>Only in Aged</td>
<td>Only in HT</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Actin-related protein 3</td>
<td>0.0</td>
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<td>2.5</td>
</tr>
<tr>
<td>Activated RNA polymerase II transcriptional coactivator p15</td>
<td>0.0</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Acyl carrier protein, mitoch.</td>
<td>0.33</td>
<td>1.0</td>
<td>only in HT</td>
</tr>
<tr>
<td>Acyl-CoA dehydrogenase family member 11</td>
<td>only in young</td>
<td>0.29</td>
<td>only in P15</td>
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<tr>
<td>Acyl-coenzyme A thioesterase 13</td>
<td>0.33</td>
<td>1.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>Acyl-coenzyme A thioesterase 2, mitoch.</td>
<td>only in young</td>
<td>0.50</td>
<td>only in P15</td>
</tr>
<tr>
<td>Acyl-coenzyme A thioesterase 4</td>
<td>only in young</td>
<td>0.50</td>
<td>only in P15</td>
</tr>
<tr>
<td>Acyl-coenzyme A thioesterase 9, mitoch.</td>
<td>only in young</td>
<td>0.50</td>
<td>only in P15</td>
</tr>
<tr>
<td>Adenylate kinase isoenzyme 1</td>
<td>only in young</td>
<td>1.1</td>
<td>0.67</td>
</tr>
<tr>
<td>Adenylate kinase isoenzyme 1</td>
<td>only in young</td>
<td>4.0</td>
<td>0.67</td>
</tr>
<tr>
<td>ADP-ribosylation factor 1</td>
<td>only in aged</td>
<td>2.5</td>
<td>only in NT</td>
</tr>
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<td>ADP-ribosylation factor 4</td>
<td>only in aged</td>
<td>2.5</td>
<td>only in NT</td>
</tr>
<tr>
<td>ADP-ribosylation factor 5</td>
<td>only in young</td>
<td>2.5</td>
<td>only in NT</td>
</tr>
<tr>
<td>AFG3-like protein 2</td>
<td>0.17</td>
<td>0.28</td>
<td>1.5</td>
</tr>
<tr>
<td>Afatoxin B1 aldehyde reductase member 2</td>
<td>only in young</td>
<td>1.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>Agrin [Parkinson disease, myocyte contraction [21;22]]</td>
<td>6.0</td>
<td>0.3</td>
<td>only in NT</td>
</tr>
<tr>
<td>A-kinase anchor protein 12 [neurodegenerative, obstructive pulmon.]</td>
<td>only in aged</td>
<td>0.3</td>
<td>only in NT</td>
</tr>
<tr>
<td>Aldehyde dehydrogenase, mitoch. [myocardial infarction, heart failure [24;25]]</td>
<td>0.35</td>
<td>1.2</td>
<td>0.93</td>
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<tr>
<td>Aldose reductase [diabetic &amp; ischemic CVD [26-28]]</td>
<td>only in aged</td>
<td>0.40</td>
<td>3.0</td>
</tr>
<tr>
<td>Aldose reductase-related protein 2</td>
<td>only in young</td>
<td>0.40</td>
<td>3.0</td>
</tr>
<tr>
<td>Alpha-2-macroglobulin [Alzheimer disease [29]]</td>
<td>3.6</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Alpha-actinin-1 [cardiomyopathy and pressure overload [30]]</td>
<td>0.55</td>
<td>0.74</td>
<td>5.9</td>
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<tr>
<td>Alpha-actinin-2 [dilated cardiomyopathy; endocardial fibroelastosis [31]]</td>
<td>0.75</td>
<td>0.71</td>
<td>19</td>
</tr>
<tr>
<td>Alpha-actinin-3 [chronic heart failure [32]]</td>
<td>only in young</td>
<td>only in NT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Alpha-actinin-4 [glomerular kidney injury [33;34]]</td>
<td>0.62</td>
<td>1.0</td>
<td>8.0</td>
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<tr>
<td>Alpha-crystallin B chain [cardiac hypertrophy; myocardial infarction [35;36]]</td>
<td>2.0</td>
<td>1.4</td>
<td>0.30</td>
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<tr>
<td>Alpha-enolase [cardiomyocyte apoptosis [37]]</td>
<td>0.09</td>
<td>0.36</td>
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<td>Alpha-internexin [Alzheimer disease [38]]</td>
<td>only in young</td>
<td>only in NT</td>
<td>only in P15</td>
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<tr>
<td>Alpha-sarcoglycan [muscular dystrophy [39]]</td>
<td>1.4</td>
<td>0.20</td>
<td>only in P15</td>
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<tr>
<td>Annexin A1 [cardioprotection in MI [40]]</td>
<td>only in HT</td>
<td>1.5</td>
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<tr>
<td>Annexin A2 [biomarker of heart failure [41]]</td>
<td>0.17</td>
<td>0.17</td>
<td>1.2</td>
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<tr>
<td>Annexin A5 [biomarker of cardiovascular risk [42]]</td>
<td>0.30</td>
<td>0.20</td>
<td>1.6</td>
</tr>
<tr>
<td>Annexin A6 [muscular dystrophy [43]]</td>
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<td>only in NT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Antithrombin-III [cardiac surgery survival; angina [44;45]]</td>
<td>only in young</td>
<td>only in HT</td>
<td>only in P15</td>
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<tr>
<td>AP-2 complex subunit beta</td>
<td>only in young</td>
<td>only in NT</td>
<td>3.2</td>
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<tr>
<td>Apolipoprotein A-1 [cardiovascular prognosis after MI [46;47]]</td>
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<td>only in NT</td>
<td>only in P15</td>
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<tr>
<td>Apolipoprotein A-IV [predictor of coronary artery disease prognosis [48;49]]</td>
<td>only in young</td>
<td>only in NT</td>
<td>only in P15</td>
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<tr>
<td>Apolipoprotein E [risk factor for atherosclerosis, Alzheimer’s, DVT [50-52]]</td>
<td>only in young</td>
<td>only in P15</td>
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</tr>
<tr>
<td>Apolipoprotein O [diabetic &amp; normal CVD, cardiac lipotoxicity [53;54]]</td>
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<td>0.43</td>
<td>only in P15</td>
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<tr>
<td>Protein Name</td>
<td>Unblasted_2</td>
<td>Unblasted_3</td>
<td>P15</td>
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<tr>
<td>----------------------------------------------------------------------------</td>
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<td>-------------</td>
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<tr>
<td>Apoptosis-inducing factor 1, mitoch. [neurodegeneration, Parkinson disease]</td>
<td>0.29</td>
<td>1.2</td>
<td>only in P15</td>
</tr>
<tr>
<td>Apoptotic chromatin condensation inducer in the nucleus</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Aquaporin-1 [cardiac edema, ischemia, hypoxia, cardioplegia(57-59)]</td>
<td>0.36</td>
<td>2.1</td>
<td>only in P15</td>
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<td>Argininosuccinate synthase [Alzheimer’s diseases(60)]</td>
<td>—</td>
<td>—</td>
<td>0.25</td>
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<tr>
<td>Arginyl-tRNA synthetase, cytoplasmic</td>
<td>only in young</td>
<td>only in NT</td>
<td>0.64</td>
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<tr>
<td>Aspartyl aminopeptidase</td>
<td>0.50</td>
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<td>—</td>
</tr>
<tr>
<td>Aspartyl/asparaginyl beta-hydroxylase</td>
<td>0.50</td>
<td>0.50</td>
<td>1.5</td>
</tr>
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<td>2.0</td>
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<tr>
<td>ATP synthase subunit alpha, mitoch.</td>
<td>0.41</td>
<td>0.97</td>
<td>1.1</td>
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<tr>
<td>ATP synthase subunit b, mitoch.</td>
<td>0.18</td>
<td>0.23</td>
<td>0.33</td>
</tr>
<tr>
<td>ATP synthase subunit beta, mitoch.</td>
<td>0.36</td>
<td>1.0</td>
<td>0.97</td>
</tr>
<tr>
<td>ATP synthase subunit d, mitoch.</td>
<td>0.10</td>
<td>0.63</td>
<td>only in P3</td>
</tr>
<tr>
<td>ATP synthase subunit e, mitoch.</td>
<td>0.65</td>
<td>0.18</td>
<td>2.0</td>
</tr>
<tr>
<td>ATP synthase subunit g, mitoch.</td>
<td>0.36</td>
<td>1.0</td>
<td>0.25</td>
</tr>
<tr>
<td>ATP synthase subunit gamma, mitoch.</td>
<td>0.46</td>
<td>0.88</td>
<td>1.3</td>
</tr>
<tr>
<td>ATPase family AAA domain-containing protein 1</td>
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<td>Only in NT</td>
<td>only in P15</td>
</tr>
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<td>ATPase family AAA domain-containing protein 3</td>
<td>0.32</td>
<td>0.18</td>
<td>0.70</td>
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<td>ATP-dependent RNA helicase DDX1</td>
<td>only in young</td>
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<td>1.8</td>
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<td>4.7</td>
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<td>ATP-dependent RNA helicase DDX3X</td>
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<td>0.77</td>
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<td>ATP-dependent RNA helicase DDX3Y</td>
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<td>only in NT</td>
<td>0.76</td>
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<tr>
<td>Atrial natriuretic factor [CVD risk factor(61;62)]</td>
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<td>only in HT</td>
<td>only in P15</td>
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<td>BAG family molecular chaperone regulator 2</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.0</td>
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<tr>
<td>BAG family molecular chaperone regulator 3</td>
<td>1.5</td>
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<td>only in P15</td>
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<tr>
<td>Barrier-to-autointegration factor</td>
<td>5.5</td>
<td>4.0</td>
<td>4.0</td>
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<tr>
<td>Barrier-to-autointegration factor</td>
<td>5.6</td>
<td>4.0</td>
<td>4.0</td>
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<tr>
<td>Basal cell adhesion molecule</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Basement membrane-specific heparan sulfate proteoglycan core protein</td>
<td>2.4</td>
<td>0.64</td>
<td>1.9</td>
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<tr>
<td>Basic leucine zipper and W2 domain-containing protein 1</td>
<td>—</td>
<td>—</td>
<td>0.29</td>
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<tr>
<td>B-cell receptor-associated protein 31</td>
<td>—</td>
<td>only in HT</td>
<td>only in P15</td>
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<tr>
<td>Beta-enolase [risk factor for cardiac surgery, acute myocardial infarction(63;64)]</td>
<td>0.30</td>
<td>0.49</td>
<td>0.87</td>
</tr>
<tr>
<td>Biglycan</td>
<td>17</td>
<td>2.0</td>
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</tr>
<tr>
<td>Bone marrow proteoglycan</td>
<td>0.50</td>
<td>only in NT</td>
<td>only in P15</td>
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<tr>
<td>Brain protein 44</td>
<td>0.43</td>
<td>0.19</td>
<td>only in P15</td>
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<tr>
<td>Brain protein 44-like protein</td>
<td>0.90</td>
<td>0.40</td>
<td>2.0</td>
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<tr>
<td>Branched-chain-amino-acid aminotransferase, mitoch.</td>
<td>only in young</td>
<td>3.5</td>
<td>only in P15</td>
</tr>
<tr>
<td>C2 domain-containing protein 3</td>
<td>only in young</td>
<td>only in NT</td>
<td>1.7</td>
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<tr>
<td>Cadherin-2 [cardiovascular development, microvascular integrity(65;66)]</td>
<td>0.43</td>
<td>0.19</td>
<td>only in P15</td>
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<tr>
<td>Calcium/calmodulin-dependent protein kinase II s. u. alpha [CVD(67;68)]</td>
<td>0.30</td>
<td>0.80</td>
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<tr>
<td>Calcium/calmodulin-dependent protein kinase II s. u. delta [cardioprotection(69)]</td>
<td>0.50</td>
<td>1.6</td>
<td>only in P15</td>
</tr>
<tr>
<td>Protein Name</td>
<td>In Young</td>
<td>In NT</td>
<td>In P15</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-------------</td>
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</tr>
<tr>
<td>Calcium-binding mitoch. carrier protein Aralar1</td>
<td>0.48</td>
<td>0.68</td>
<td>0.75</td>
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<tr>
<td>Calcium-binding mitoch. carrier protein Aralar2</td>
<td>0.37</td>
<td>0.88</td>
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<tr>
<td>Calnexin [cardiomyocyte ER stress, apoptosis(70)]</td>
<td>only in young</td>
<td>only in NT</td>
<td>1.7</td>
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<tr>
<td>Calponin-2 [vascular development(71)]</td>
<td>only in young</td>
<td>only in NT</td>
<td>1.3</td>
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<tr>
<td>Calnexin-2 ([72-74])</td>
<td>0.42</td>
<td>1.3</td>
<td>only in P15</td>
</tr>
<tr>
<td>Calumenin [dilated cardiomyopathy(75)]</td>
<td>only in young</td>
<td>only in HT</td>
<td>7.5</td>
</tr>
<tr>
<td>cAMP-dep’t protein kinase catalytic s. u. beta [energy balance, cardiac</td>
<td>only in young</td>
<td>0.25</td>
<td>only in P15</td>
</tr>
<tr>
<td>CAMP-dependent protein kinase type II-alpha regulatory subunit</td>
<td>only in young</td>
<td>Only in NT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Carbonic anhydrase 2 [cardiac changes with age(78)]</td>
<td>only in young</td>
<td>2.7</td>
<td>only in P15</td>
</tr>
<tr>
<td>Cardiac phospholamban [heart failure(79)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Carnitine O-acetyltransferase</td>
<td>0.05</td>
<td>0.10</td>
<td>only in P15</td>
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<tr>
<td>Carnitine O-palmitoyltransferase, mitoch.</td>
<td>0.07</td>
<td>0.71</td>
<td>only in P15</td>
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<tr>
<td>Casein kinase isoform alpha</td>
<td>0.50</td>
<td>only in NT</td>
<td>1.5</td>
</tr>
<tr>
<td>Catalase [coronary heart disease(80)]</td>
<td>3.0</td>
<td>0.50</td>
<td>only in P15</td>
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<tr>
<td>Catenin alpha-1</td>
<td>0.80</td>
<td>0.29</td>
<td>6.5</td>
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<tr>
<td>Catenin alpha-3</td>
<td>0.81</td>
<td>0.27</td>
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<tr>
<td>Catenin beta-1</td>
<td>1.60</td>
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<td>only in P15</td>
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<td>Cathepsin D</td>
<td>—</td>
<td>only in HT</td>
<td>0.75</td>
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<tr>
<td>Caveolin-1</td>
<td>0.96</td>
<td>3.4</td>
<td>0.75</td>
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<td>Caveolin-2</td>
<td>0.50</td>
<td>1.5</td>
<td>only in P15</td>
</tr>
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<td>Caveolin-3</td>
<td>1.00</td>
<td>7.0</td>
<td>only in P3</td>
</tr>
<tr>
<td>CDS antigen-like</td>
<td>3.0</td>
<td>1.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>CDGSH iron sulfur domain-containing protein 1</td>
<td>only in young</td>
<td>3.5</td>
<td>only in P15</td>
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<tr>
<td>CDGSH iron sulfur domain-containing protein 3, mitoch.</td>
<td>0.67</td>
<td>0.33</td>
<td>only in P15</td>
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<tr>
<td>CDP-diaclyglycerol-inositol 3-phosphatidytransferase</td>
<td>only in young</td>
<td>—</td>
<td>only in P15</td>
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<tr>
<td>Cell division control protein 42 homolog</td>
<td>0.50</td>
<td>0.25</td>
<td>1.0</td>
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<tr>
<td>Cell division protein kinase 13</td>
<td>1.10</td>
<td>3.6</td>
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<tr>
<td>Centromere protein V</td>
<td>only in aged</td>
<td>0.20</td>
<td>only in P15</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>only in aged</td>
<td>only in HT</td>
<td>—</td>
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<tr>
<td>Chaperone activity of bc1 complex-like, mitoch.</td>
<td>7.50</td>
<td>0.13</td>
<td>only in P15</td>
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<tr>
<td>Chromobox protein homolog 3</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.7</td>
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<td>Chymase</td>
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<td>0.50</td>
<td>only in P15</td>
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<tr>
<td>Clathrin heavy chain 1</td>
<td>2.40</td>
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<td>1.6</td>
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<tr>
<td>Clathrin light chain A</td>
<td>only in aged</td>
<td>only in HT</td>
<td>7.0</td>
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<tr>
<td>Clusterin [clearance of misfolded proteins(81;82)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
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<tr>
<td>Coatomer subunit alpha</td>
<td>only in aged</td>
<td>only in HT</td>
<td>0.50</td>
</tr>
<tr>
<td>Coatomer subunit beta</td>
<td>only in aged</td>
<td>only in HT</td>
<td>5.0</td>
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<tr>
<td>Cofilin-1</td>
<td>2.00</td>
<td>0.75</td>
<td>1.3</td>
</tr>
<tr>
<td>Cofilin-2</td>
<td>1.50</td>
<td>2.3</td>
<td>1.1</td>
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<tr>
<td>Coiled-coil-helix-coiled-helix domain-containing protein 3, mitoch.</td>
<td>0.25</td>
<td>15</td>
<td>only in P15</td>
</tr>
<tr>
<td>Protein Name</td>
<td>Expression in</td>
<td>Expression in</td>
<td>Expression in</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
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<tr>
<td>Coiled-coil-helix-coiled-coil-helix domain-containing protein 6</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
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<tr>
<td>Collagen alpha-1(I) chain</td>
<td>2.4</td>
<td>0.15</td>
<td>1.1</td>
</tr>
<tr>
<td>Collagen alpha-1(III) chain</td>
<td>only in aged</td>
<td>only in NT</td>
<td>1.2</td>
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<tr>
<td>Collagen alpha-1(IV) chain</td>
<td>0.48</td>
<td>only in NT</td>
<td>only in P15</td>
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<td>Collagen alpha-1(VI) chain</td>
<td>0.47</td>
<td>0.85</td>
<td>3.0</td>
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<tr>
<td>Collagen alpha-1(VII) chain</td>
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<td>only in NT</td>
<td>only in P15</td>
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<tr>
<td>Collagen alpha-1(XII) chain</td>
<td>only in aged</td>
<td>only in HT</td>
<td>9.9</td>
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<tr>
<td>Collagen alpha-1(XV) chain</td>
<td>0.14</td>
<td>only in NT</td>
<td>only in P15</td>
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<tr>
<td>Collagen alpha-2(I) chain</td>
<td>2.1</td>
<td>0.15</td>
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<td>Collagen alpha-2(IV) chain</td>
<td>0.51</td>
<td>0.09</td>
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<td>Collagen alpha-2(VI) chain</td>
<td>0.45</td>
<td>0.62</td>
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<td>Collagen alpha-3(IV) chain</td>
<td>0.83</td>
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<td>only in P15</td>
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<td>Collagen alpha-6(VI) chain</td>
<td>0.38</td>
<td>0.67</td>
<td>only in P15</td>
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<tr>
<td>Complement C1q subcomponent subunit A [angiogenesis, wound healing(83)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
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<tr>
<td>Complement C1q subcomponent subunit B</td>
<td>3.0</td>
<td>1.5</td>
<td>only in P15</td>
</tr>
<tr>
<td>Complement C3 [cardiometabolic risk, Alzheimer disease(84-87)]</td>
<td>14</td>
<td>1.5</td>
<td>only in P15</td>
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<tr>
<td>Complement C4-B [myocardial infarction(88)]</td>
<td>5.0</td>
<td>1.0</td>
<td>only in P15</td>
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<tr>
<td>Complement component 1 Q subcomponent-binding protein, mitoch.</td>
<td>only in aged</td>
<td>5.0</td>
<td>only in P15</td>
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<tr>
<td>Core histone macro-H2A.1 [Huntington disease(89)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.3</td>
</tr>
<tr>
<td>Core histone macro-H2A.2 [Huntington disease(89)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.7</td>
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<tr>
<td>Coronin-1B</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.0</td>
</tr>
<tr>
<td>Coronin-6</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Creatine kinase B-type [ventricular arrhythmia(90;91)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
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<tr>
<td>Creatine kinase M-type</td>
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<td>0.70</td>
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<tr>
<td>CTP synthase 1</td>
<td>only in young</td>
<td>only in HT</td>
<td>0.40</td>
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<tr>
<td>Cullin-associated NEDD8-dissociated protein 1</td>
<td>only in young</td>
<td>only in HT</td>
<td>3.0</td>
</tr>
<tr>
<td>Cullin-associated NEDD8-dissociated protein 2</td>
<td>only in young</td>
<td>14</td>
<td>only in P15</td>
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<tr>
<td>Cysteine and glycine-rich protein 1</td>
<td>only in young</td>
<td>only in HT</td>
<td>6.0</td>
</tr>
<tr>
<td>Cytochrome b5 type B</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.0</td>
</tr>
<tr>
<td>Cytochrome b-c1 complex subunit 1, mitoch.</td>
<td>6.7</td>
<td>1.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Cytochrome b-c1 complex subunit 2, mitoch.</td>
<td>9.8</td>
<td>2.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Cytochrome b-c1 complex subunit 6, mitoch.</td>
<td>1.0</td>
<td>3.5</td>
<td>only in P15</td>
</tr>
<tr>
<td>Cytochrome b-c1 complex subunit 8</td>
<td>5.0</td>
<td>4.0</td>
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</tr>
<tr>
<td>Cytochrome b-c1 complex subunit 9</td>
<td>4.0</td>
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</tr>
<tr>
<td>Cytochrome b-c1 complex subunit Rieske, mitoch.</td>
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<td>2.4</td>
<td>only in P15</td>
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<tr>
<td>Cytochrome c oxidase subunit 2</td>
<td>2.0</td>
<td>4.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Cytochrome c oxidase subunit 3</td>
<td>only in aged</td>
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<td>only in P15</td>
</tr>
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<td>Cytochrome c oxidase subunit 4 isoform 1, mitoch.</td>
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<td>2.0</td>
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<tr>
<td>Cytochrome c oxidase subunit 5A, mitoch.</td>
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<td>Cytochrome c oxidase subunit 5B, mitoch.</td>
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<td>3.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Protein Name</td>
<td>Expression Pattern</td>
<td>Value</td>
<td>Value</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Cytochrome c oxidase subunit 6A1, mitoch.</td>
<td>only in aged</td>
<td>0.23</td>
<td>only in HT</td>
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<tr>
<td>Cytochrome c oxidase subunit 6B1</td>
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<tr>
<td>Cytochrome c oxidase subunit 6C</td>
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<td>4.3</td>
</tr>
<tr>
<td>Cytochrome c oxidase subunit 7A1, mitoch.</td>
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<td>3.2</td>
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</tr>
<tr>
<td>Cytochrome c oxidase subunit 7A2, mitoch.</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
</tr>
<tr>
<td>Cytochrome c oxidase subunit 7C, mitoch.</td>
<td>only in aged</td>
<td>1.5</td>
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</tr>
<tr>
<td>Cytochrome c oxidase subunit 7C [apoptosis, ensuing from myocardial ischaemia(92;93)]</td>
<td>2.0</td>
<td>6.0</td>
<td>2.5</td>
</tr>
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<td>Cytochrome c1, heme protein, mitoch.</td>
<td>29</td>
<td>2.1</td>
<td>only in P15</td>
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<tr>
<td>Cytoplasmic dynein 1 heavy chain 1</td>
<td>9.0</td>
<td>0.89</td>
<td>1.4</td>
</tr>
<tr>
<td>Cytoplasmic dynein 1 intermediate chain 2</td>
<td>only in aged</td>
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<td>only in HT</td>
</tr>
<tr>
<td>Cytoskeleton-associated protein 4</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
</tr>
<tr>
<td>Cytoskeleton-associated protein 5</td>
<td>only in aged</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Cytosol aminopeptidase</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
</tr>
<tr>
<td>Cytosolic acyl coenzyme A thioester hydrolase</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
</tr>
<tr>
<td>D-beta-hydroxybutyrate dehydrogenase, mitoch.</td>
<td>0.05</td>
<td>24</td>
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<tr>
<td>Decorin</td>
<td>2.0</td>
<td>1.3</td>
<td>only in P15</td>
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<tr>
<td>Dehydrogenase/reductase SDR family member 4</td>
<td>only in aged</td>
<td>1.0</td>
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<tr>
<td>Delta-1-pyrroline-5-carboxylate dehydrogenase, mitoch.</td>
<td>4.5</td>
<td>0.78</td>
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<tr>
<td>Delta-1-pyrroline-5-carboxylate synthase</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
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<tr>
<td>Dermatopontin</td>
<td>0.56</td>
<td>0</td>
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<td>Dihydricipicolinate synthase-like, mitoch.</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
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<td>Dihydrolipoyl dehydrogenase, mitoch.</td>
<td>1.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Dihydropyrimidinase-related protein 1</td>
<td>only in young</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Dihydropyrimidinase-related protein 2</td>
<td>only in aged</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Dihydropyrimidinase-related protein 3</td>
<td>0.67</td>
<td>0.33</td>
<td>2.7</td>
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<tr>
<td>DNA helicase B</td>
<td>0.63</td>
<td>0.25</td>
<td>0.33</td>
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<tr>
<td>DNA topoisomerase 2-alpha</td>
<td>only in aged</td>
<td></td>
<td></td>
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<tr>
<td>DNA topoisomerase 2-beta</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
</tr>
<tr>
<td>DNA-(apurinic or apyrimidinic site) lyase</td>
<td>only in aged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA-binding protein A</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
</tr>
<tr>
<td>DnaJ homolog subfamily A member 1</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
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<tr>
<td>DnaJ homolog subfamily C member 10</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
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<tr>
<td>Dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit STT3A</td>
<td>2.0</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Drebrin</td>
<td>only in aged</td>
<td></td>
<td>only in HT</td>
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<tr>
<td>Dynamin-1 [cardiomyopathy (94)]</td>
<td>1.0</td>
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<tr>
<td>Dynamin-1-like protein [cardiachypertrophy, heart failure(95;96)]</td>
<td>only in aged</td>
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<td>only in NT</td>
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<tr>
<td>Dynamin-like 120 kDa protein, mitoch.</td>
<td>31</td>
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<tr>
<td>Dynemin light chain 1, cytoplasmic</td>
<td>0.75</td>
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<tr>
<td>Dynemin light chain 2, cytoplasmic</td>
<td>0.57</td>
<td>0.75</td>
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<tr>
<td>Dynemin light chain roadblock-type 1</td>
<td>only in young</td>
<td></td>
<td>only in HT</td>
</tr>
<tr>
<td>Protein Name</td>
<td>Young</td>
<td>HT</td>
<td>NT</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
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</tr>
<tr>
<td>E3 ubiquitin-protein ligase NEDD4 [cardioprotection(97)]</td>
<td>—</td>
<td>only in HT</td>
<td>0.83</td>
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<tr>
<td>EH domain-containing protein 1</td>
<td>only in young</td>
<td>only in NT</td>
<td>0.75</td>
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<tr>
<td>EH domain-containing protein 2 [cardiac membrane protein targeting(98)]</td>
<td>only in young</td>
<td>only in NT</td>
<td>0.14</td>
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<tr>
<td>EH domain-containing protein 4</td>
<td>16</td>
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<td>only in P15</td>
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<tr>
<td>Electron transfer flavoprotein subunit alpha, mitoch.</td>
<td>0.22</td>
<td>0.87</td>
<td>0.82</td>
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<tr>
<td>Electron transfer flavoprotein subunit beta</td>
<td>6</td>
<td>0.94</td>
<td>0.5</td>
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<tr>
<td>Electron transfer flavoprotein-ubiquinone oxireductase, mitoch.</td>
<td>5.1</td>
<td>0.37</td>
<td>only in P15</td>
</tr>
<tr>
<td>Elongation factor 1-beta</td>
<td>only in aged</td>
<td>only in HT</td>
<td>3.0</td>
</tr>
<tr>
<td>Elongation factor 1-delta</td>
<td>only in aged</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Elongation factor 2 [pathologic angiogenesis(99;100)]</td>
<td>3.0</td>
<td>0.5</td>
<td>1.1</td>
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<td>Elongation factor Tu, mitoch.</td>
<td>0.47</td>
<td>0.70</td>
<td>0.46</td>
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<td>EMILIN-1</td>
<td>0.11</td>
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<td>only in P15</td>
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<td>Endoplasmic reticulum resident protein 29</td>
<td>only in aged</td>
<td>only in HT</td>
<td>3.0</td>
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<tr>
<td>Endoplasmin</td>
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<td>—</td>
<td>1.1</td>
</tr>
<tr>
<td>Enhancer of rudimentary homolog</td>
<td>—</td>
<td>—</td>
<td>16</td>
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<td>Enoyl-CoA hydratase, mitoch.</td>
<td>2.4</td>
<td>0.71</td>
<td>only in P3</td>
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<tr>
<td>Epiplakin</td>
<td>0.75</td>
<td>0.5</td>
<td>only in P15</td>
</tr>
<tr>
<td>Erlin-1 [Alzheimer Disease(101;102)]</td>
<td>—</td>
<td>—</td>
<td>only in P3</td>
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<td>ES1 protein homolog, mitoch.</td>
<td>3.0</td>
<td>1.3</td>
<td>only in P15</td>
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<td>Eukaryotic translation initiation factor 1A</td>
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<td>only in HT</td>
<td>3.0</td>
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<tr>
<td>Eukaryotic translation initiation factor 2 subunit 1</td>
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<td>2.0</td>
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<tr>
<td>Eukaryotic translation initiation factor 2 subunit 3, X-linked</td>
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<td>only in HT</td>
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<td>Eukaryotic translation initiation factor 3 subunit E</td>
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<td>Eukaryotic translation initiation factor 5A-1</td>
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<td>1.1</td>
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<td>Exportin-2</td>
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<td>1.7</td>
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<td>Extended synaptotagmin-1</td>
<td>only in aged</td>
<td>only in HT</td>
<td>3.0</td>
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<td>Ezrin [endothelial barrier function, nitric oxide production(103;104)]</td>
<td>1.0</td>
<td>—</td>
<td>1.56</td>
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<td>FACT complex subunit SPT16</td>
<td>only in aged</td>
<td>only in HT</td>
<td>3.3</td>
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<td>F-actin-capping protein subunit alpha-1</td>
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<td>only in HT</td>
<td>0.86</td>
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<td>F-actin-capping protein subunit alpha-2</td>
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<td>F-actin-capping protein subunit beta</td>
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<td>1.8</td>
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<td>Fascin</td>
<td>only in aged</td>
<td>only in HT</td>
<td>11</td>
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<td>Fatty acid synthase</td>
<td>—</td>
<td>only in HT</td>
<td>2.3</td>
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<tr>
<td>Fatty acid-binding protein, adipocyte [renal dysfunction, heart failure(105;106)]</td>
<td>1.2</td>
<td>0.42</td>
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<td>Fatty acid-binding protein, heart [risk factor for acute coronary syndromes(107)]</td>
<td>2.2</td>
<td>0.45</td>
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<td>Fermitin family homolog 2</td>
<td>only in aged</td>
<td>only in HT</td>
<td>3</td>
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<tr>
<td>Ferritin heavy chain</td>
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<td>Ferritin light chain 1</td>
<td>9.1</td>
<td>10</td>
<td>0.37</td>
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<tr>
<td>Fibrillin-1 [CVD(108)]</td>
<td>2.3</td>
<td>0.88</td>
<td>only in P15</td>
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<td>Fibrillin-2</td>
<td>3.3</td>
<td>1.3</td>
<td>only in P15</td>
</tr>
<tr>
<td>Protein</td>
<td>Ratio</td>
<td>Standard Deviation</td>
<td>Condition</td>
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<td>------------------------------------------------------------------------</td>
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<td>--------------------</td>
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</tr>
<tr>
<td>Fibrinogen beta chain</td>
<td>1.9</td>
<td>0.29</td>
<td>only in P15</td>
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<tr>
<td>Fibrinogen gamma chain</td>
<td>1.2</td>
<td>0.21</td>
<td>only in P15</td>
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<tr>
<td>Fibronectin [congenital heart disease(109)]</td>
<td>4.6</td>
<td>1.2</td>
<td>0.78</td>
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<tr>
<td>Filamin-A</td>
<td>3.4</td>
<td>4.0</td>
<td>2.1</td>
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<tr>
<td>Filamin-B [cardiovascular development(110)]</td>
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<td></td>
<td>only in aged only in HT 2.41</td>
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<tr>
<td>Filamin-C [heart failure(111)]</td>
<td>3.5</td>
<td>2.7</td>
<td>2.3</td>
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<td>Four and a half LIM domains protein 2</td>
<td>1.1</td>
<td>1.2</td>
<td>only in P15</td>
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<td>Fragile X mental retardation protein 1 homolog</td>
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<td>only in aged only in HT 1.3</td>
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<td>Fragile X mental retardation syndrome-related protein 1</td>
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<td></td>
<td>only in aged only in HT 1.5</td>
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<td>Fructose-bisphosphate aldolase B</td>
<td></td>
<td></td>
<td>only in aged only in HT 0.29</td>
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<td>Fumarate hydratase, mitoch.</td>
<td>6.3</td>
<td>0.37</td>
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<td>Galectin-1</td>
<td>2.0</td>
<td>4.0</td>
<td>2.4</td>
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<td>Gamma-enolase [serum risk factor after cardiac arrest(112)]</td>
<td></td>
<td></td>
<td>only in young only in NT —</td>
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<tr>
<td>Gamma-glutamyln transeptidase 1</td>
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<td></td>
<td>only in aged only in HT only in P15</td>
</tr>
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<td>Gap junction alpha-1 protein</td>
<td>1.2</td>
<td>0.48</td>
<td>only in P15</td>
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<td>Gelsolin</td>
<td>0.27</td>
<td>1.1</td>
<td>3.0</td>
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<td>General vesicular transport factor p115</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
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<td>Glial fibrillary acidic protein [congenital heart disease(113)]</td>
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<tr>
<td>Glucosamine-fructose-6-phosphate aminotransferase [isomerizing] 1</td>
<td></td>
<td></td>
<td>only in aged only in HT 0.33</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase 2 [CVD(114;115)]</td>
<td></td>
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<td>only in aged — 2.5</td>
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<tr>
<td>Glucose-6-phosphate isomerase</td>
<td>1.1</td>
<td>1.3</td>
<td>6.3</td>
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<tr>
<td>Glutamate dehydrogenase 1, mitoch.</td>
<td></td>
<td></td>
<td>only in aged — 1.4</td>
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<tr>
<td>Glutaredoxin-3</td>
<td></td>
<td></td>
<td>only in aged only in NT 0.22</td>
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<tr>
<td>Glutathione peroxidase 1</td>
<td>1.8</td>
<td>2</td>
<td>0.94</td>
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<tr>
<td>Glutathione S-transferase A2 [coronary heart disease, oxidative stress(116)]</td>
<td></td>
<td></td>
<td>only in aged only in HT only in P15</td>
</tr>
<tr>
<td>Glutathione S-transferase k1</td>
<td></td>
<td></td>
<td>only in young only in NT 0.40</td>
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<tr>
<td>Glutathione S-transferase Mu 1</td>
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<td>only in aged only in HT only in P15</td>
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<tr>
<td>Glutathione S-transferase omega-1 [cerebrovascular atherosclerosis(117)]</td>
<td></td>
<td></td>
<td>only in aged only in HT 4.2</td>
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<tr>
<td>Glutathione S-transferase P 1</td>
<td>1</td>
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<td>2.0</td>
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<tr>
<td>Glyceraldehyde-3-phosphate dehydrogenase [cardiomyocyte apoptosis(118)]</td>
<td>0.67</td>
<td>0.50</td>
<td>1.4</td>
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<tr>
<td>Glycerol kinase</td>
<td></td>
<td></td>
<td>only in aged only in HT only in P15</td>
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<tr>
<td>Glycerol-3-phosphate dehydrogenase, mitoch.</td>
<td></td>
<td></td>
<td>only in aged only in HT 2.5</td>
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<tr>
<td>Glycogen phosphorylase, brain form [CVD risk factor(119)]</td>
<td></td>
<td></td>
<td>only in young 0.44 20</td>
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<tr>
<td>Glycogen phosphorylase, muscle form [CVD risk factor(119)]</td>
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<td>0.24</td>
<td>4.0</td>
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<tr>
<td>Glyoxalase domain-containing protein 4</td>
<td></td>
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<td>only in aged only in HT 4.0</td>
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<td>GMP reductase 1</td>
<td></td>
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<td>only in aged 3.0 only in P15</td>
</tr>
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<td>Golgi apparatus protein 1</td>
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<td></td>
<td>only in aged only in HT 2.5</td>
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<td>Granulins</td>
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<td></td>
<td>only in aged only in HT 0.40</td>
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<td>GTP:AMP phosphotransferase mitoch.</td>
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<td>only in aged only in HT 0.40</td>
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<tr>
<td>GTP-binding nuclear protein Ran</td>
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<td></td>
<td>only in aged only in HT 0.94</td>
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<tr>
<td>Protein Name</td>
<td>Expression Pattern</td>
<td>Magnitude</td>
<td>Reference</td>
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<tr>
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<td>GTP-binding protein SAR1b</td>
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<td>only in P15</td>
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<tr>
<td>Guanine nucleotide-binding protein G(i) subunit alpha-2</td>
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<tr>
<td>Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-12</td>
<td>Only in aged</td>
<td>only in HT</td>
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<td>Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-5</td>
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<td>only in HT</td>
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<tr>
<td>Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1</td>
<td>0.25</td>
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<tr>
<td>Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2</td>
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<tr>
<td>Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas</td>
<td>1.25</td>
<td>only in NT</td>
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<td>Guanine nucleotide-binding protein subunit beta-2-like 1</td>
<td>only in aged</td>
<td>only in HT</td>
<td>1.4</td>
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<td>H/ACA ribonucleoprotein complex subunit 4</td>
<td>only in aged</td>
<td>only in HT</td>
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<td>H-2 class I histocompatibility antigen, D-B alpha chain</td>
<td>6.0</td>
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<td>only in P15</td>
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<tr>
<td>H-2 class I histocompatibility antigen, K-B alpha chain</td>
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<td>—</td>
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<tr>
<td>H-2 class I histocompatibility antigen, Q8 alpha chain</td>
<td>only in aged</td>
<td>—</td>
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</tr>
<tr>
<td>Heat shock 70 kDa protein 12A [CVD, Alzheimer Disease(120;121)]</td>
<td>only in young</td>
<td>0.33</td>
<td>only in P15</td>
</tr>
<tr>
<td>Heat shock 70 kDa protein 12B [CVD, Alzheimer Disease(120;121)]</td>
<td>0.67</td>
<td>only in NT</td>
<td>only in P15</td>
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<tr>
<td>Heat shock protein 75 kDa, mitoch. [CNS focal ischaemia(122)]</td>
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<td>only in NT</td>
<td>0.50</td>
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<tr>
<td>Heat shock protein beta-6 [Aging(123)]</td>
<td>2.3</td>
<td>only in NT</td>
<td>only in P15</td>
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<td>Heat shock protein beta-7</td>
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<td>only in NT</td>
<td>only in P15</td>
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<td>Heat shock protein beta-8</td>
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<td>Heat shock protein HSP 90-alpha [Alzheimer Disease, other tauopathies]</td>
<td>0.26</td>
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<td>0.69</td>
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<td>Hemoglobin subunit alpha</td>
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<td>0.75</td>
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<td>Hemopexin</td>
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<td>Heterogeneous nuclear ribonucleoprotein A/B</td>
<td>only in aged</td>
<td>only in HT</td>
<td>3.0</td>
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<td>Heterogeneous nuclear ribonucleoprotein A3</td>
<td>only in aged</td>
<td>only in HT</td>
<td>4.8</td>
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<td>Heterogeneous nuclear ribonucleoprotein H</td>
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<td>Heterogeneous nuclear ribonucleoprotein L</td>
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<tr>
<td>Heterogeneous nuclear ribonucleoprotein M</td>
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<td>Heterogeneous nuclear ribonucleoproteins A2/B1</td>
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<td>Heterogeneous nuclear ribonucleoproteins C1/C2</td>
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<td>only in HT</td>
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<tr>
<td>Hexokinase-1</td>
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<td>Protein Name</td>
<td>Expression</td>
<td>Value 1</td>
<td>Value 2</td>
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<td>High mobility group protein B1</td>
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<td></td>
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<tr>
<td>High mobility group protein HMG-I/HMG-Y</td>
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<tr>
<td>High mobility group protein HMGI-C</td>
<td>only in aged</td>
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<tr>
<td>Histone H1t [Alzheimer Disease(126)]</td>
<td>only in aged</td>
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<tr>
<td>Histone H1.1 [Neurodegenerative diseases(127)]</td>
<td>only in aged</td>
<td>1.5</td>
<td>0.50</td>
</tr>
<tr>
<td>Histone H1.2</td>
<td>only in aged</td>
<td>2.0</td>
<td>0.94</td>
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<tr>
<td>Histone H1.3</td>
<td>only in aged</td>
<td>1.9</td>
<td>0.82</td>
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<tr>
<td>Histone H1.4 [Alzheimer disease(128)]</td>
<td>only in aged</td>
<td>2.3</td>
<td>0.91</td>
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<tr>
<td>Histone H1.5</td>
<td>only in aged</td>
<td>1.9</td>
<td>0.44</td>
</tr>
<tr>
<td>Histone H2A type 2-B [Huntington disease(129)]</td>
<td>only in aged</td>
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<tr>
<td>Histone H2A.V</td>
<td>only in aged</td>
<td>3.5</td>
<td>2.5</td>
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<tr>
<td>Histone H2A.x</td>
<td>only in aged</td>
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<td>2.0</td>
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<td>Histone H2B type 2-E</td>
<td>only in aged</td>
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<td>Histone H3.1</td>
<td>only in aged</td>
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<td>1.2</td>
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<td>only in aged</td>
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<td>1.2</td>
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<td>Histone H3.3</td>
<td>only in aged</td>
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<td>0.92</td>
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<td>Histone H4</td>
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<td>1.4</td>
<td>0.49</td>
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<tr>
<td>Hydrocephalus-inducing protein</td>
<td>only in aged</td>
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<tr>
<td>Hydroxyacyl-coenzyme A dehydrogenase, mitoch.</td>
<td>only in aged</td>
<td>0.11</td>
<td>1.0</td>
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<tr>
<td>Ig alpha chain C region</td>
<td>only in aged</td>
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<tr>
<td>Ig gamma-1 chain C region secreted form</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ig gamma-2A chain C region, A allele</td>
<td>only in aged</td>
<td>8.7</td>
<td>0.71</td>
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<td>Ig gamma-2B chain C region</td>
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<td>2.3</td>
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<tr>
<td>Ig heavy chain V region AC38205.12</td>
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<td>Ig kappa chain C region</td>
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<td>Ig kappa chain V-ll region 26-10</td>
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<td>Ig lambda-1 chain C region</td>
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<td>Ig mu chain C region secreted form</td>
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<td>0.67</td>
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<td>Immunity-related GTPase family M protein</td>
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<tr>
<td>Immunoglobulin J chain</td>
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<td>Importin subunit beta-1</td>
<td>only in aged</td>
<td>0.43</td>
<td>1.27</td>
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<td>Inosine-5’-monophosphate dehydrogenase 2</td>
<td>only in aged</td>
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<tr>
<td>Integrin alpha-5</td>
<td>only in aged</td>
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<tr>
<td>Integrin beta-1</td>
<td>only in aged</td>
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<td>Integrin-linked protein kinase</td>
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<td>Interferon-inducible GTPase 1</td>
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<td>Interleukin enhancer-binding factor 3</td>
<td>only in aged</td>
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<td>3.5</td>
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<td>Isobutyryl-CoA dehydrogenase, mitoch.</td>
<td>only in aged</td>
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<tr>
<td>Isocitrate dehydrogenase [NAD] subunit alpha, mitoch.</td>
<td>only in aged</td>
<td>0.19</td>
<td>0.78</td>
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<tr>
<td></td>
<td>0.13</td>
<td>2.0</td>
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<tr>
<td>Protein Name</td>
<td>Expression Pattern</td>
<td>Age 1</td>
<td>Age 2</td>
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<td>-----------------------------------------------------------------------------</td>
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<td>Isocitrate dehydrogenase [NAD] subunit gamma, mitoch.</td>
<td>only in young</td>
<td>0.40</td>
<td>0.11</td>
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<td>Isocitrate dehydrogenase [NADP], mitoch.</td>
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<td>0.17</td>
<td>0.31</td>
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<tr>
<td>Isoleucyl-tRNA synthetase, cytoplasmic</td>
<td>only in aged</td>
<td>only in HT</td>
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<tr>
<td>Isoleucyl-tRNA synthetase, mitoch.</td>
<td>only in aged</td>
<td>only in HT</td>
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<tr>
<td>Junction plakoglobin</td>
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<td>1.3</td>
<td>0.39</td>
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<tr>
<td>Junctophilin-2 [cardiocyte hypertrophy(130)]</td>
<td>only in young</td>
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<tr>
<td>Keratin, type I cuticular Hα5</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in HT</td>
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<tr>
<td>Keratin, type I cytoskeletal 13</td>
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<td>0.98</td>
<td>0.39</td>
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<tr>
<td>Keratin, type I cytoskeletal 15</td>
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<tr>
<td>Keratin, type I cytoskeletal 17</td>
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<td>0.44</td>
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<tr>
<td>Keratin, type I cytoskeletal 40</td>
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<tr>
<td>Keratin, type I cytoskeletal 42</td>
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<td>1.4</td>
<td>0.39</td>
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<tr>
<td>Keratin, type II cytoskeletal 4</td>
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<td>only in NT</td>
<td>only in NT</td>
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<tr>
<td>Keratin, type II cuticular Hb4</td>
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<td>only in young</td>
<td>only in NT</td>
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<tr>
<td>Keratin, type II cytoskeletal 1b</td>
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<td>Keratin, type II cytoskeletal 2 epidermal</td>
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<td>0.37</td>
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<td>Keratin, type II cytoskeletal 2 oral</td>
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<tr>
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<tr>
<td>Keratin, type II cytoskeletal 5</td>
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<td>0.72</td>
<td>0.33</td>
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<tr>
<td>Keratin, type II cytoskeletal 6A</td>
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<td>0.73</td>
<td>0.47</td>
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<td>Keratin, type II cytoskeletal 7</td>
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<td>0.84</td>
<td>0.43</td>
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<tr>
<td>Keratin, type II cytoskeletal 72</td>
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<tr>
<td>Keratin, type II cytoskeletal 73</td>
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<td>0.84</td>
<td>0.43</td>
</tr>
<tr>
<td>Keratin, type II cytoskeletal 74</td>
<td>only in young</td>
<td>only in NT</td>
<td>only in NT</td>
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<td>Keratin, type II cytoskeletal 75</td>
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<td>0.50</td>
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<td>Keratin, type II cytoskeletal 79</td>
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<td>0.81</td>
<td>0.39</td>
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<td>Keratin, type II cytoskeletal 8</td>
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<td>0.80</td>
<td>0.27</td>
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<tr>
<td>Kinectin</td>
<td></td>
<td>only in aged</td>
<td>only in HT</td>
</tr>
<tr>
<td>Kinesin heavy chain isoform 5A</td>
<td>only in young</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Kinesin-1 heavy chain</td>
<td>only in young</td>
<td>6.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Kininogen-1</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>KN motif and ankyrin repeat domain-containing protein 2</td>
<td></td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Lamin-A/C [Several inherited diseases(131)]</td>
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<td>2.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Lamina-associated polypeptide 2, isoforms beta/delta/epsilon/gamma</td>
<td>only in young</td>
<td>only in HT</td>
<td></td>
</tr>
<tr>
<td>Lamin-B1</td>
<td></td>
<td>0.29</td>
<td>1.1</td>
</tr>
<tr>
<td>Lamin-B2</td>
<td>only in aged</td>
<td>only in HT</td>
<td></td>
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<tr>
<td>Laminin subunit alpha-2 [Hypertrophic myocardium(132)]</td>
<td></td>
<td>1.8</td>
<td>0.66</td>
</tr>
<tr>
<td>Laminin subunit alpha-4 [cardiomyopathy (133)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Laminin subunit alpha-5 [tumor invasion, angiogenesis &amp;metastasis(134)]</td>
<td>only in NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laminin subunit beta-1</td>
<td></td>
<td>1.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Laminin subunit beta-2 [muscular dystrophy(135)]</td>
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<td>2.0</td>
<td>0.72</td>
</tr>
<tr>
<td>Protein Name</td>
<td>Change</td>
<td>pValue</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>----------</td>
<td>----------</td>
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</tr>
<tr>
<td>Laminin subunit gamma-1 [Alzheimer disease][136]</td>
<td>1.7</td>
<td>0.95</td>
<td>—</td>
</tr>
<tr>
<td>LETM1 and EF-hand domain-containing protein 1, mitoch.</td>
<td>only in young</td>
<td>only in NT</td>
<td>—</td>
</tr>
<tr>
<td>Leucine-rich PPR motif-containing protein, mitoch. [Gastric Cancer][137;138]</td>
<td>only in young</td>
<td>0.24</td>
<td>1.0</td>
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<tr>
<td>LIM domain binding protein 3</td>
<td>0.86</td>
<td>0.78</td>
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<tr>
<td>Lipoamide acyltransferase component of branched-chain alpha-keto acid</td>
<td>0.50</td>
<td>1.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>Lipoprotein lipase [risk factor, ischemic stroke &amp; coronary heart disease][139]</td>
<td>4.6</td>
<td>0.17</td>
<td>only in P15</td>
</tr>
<tr>
<td>Lon protease homolog, mitoch.</td>
<td>only in young</td>
<td>0.20</td>
<td>—</td>
</tr>
<tr>
<td>Long-chain specific acyl-CoA dehydrogenase, mitoch.</td>
<td>1.2</td>
<td>1.4</td>
<td>0.50</td>
</tr>
<tr>
<td>Low molecular weight phosphotyrosine protein phosphatase [diabetes][142]</td>
<td>0.44</td>
<td>0.22</td>
<td>only in P3</td>
</tr>
<tr>
<td>MACRO domain-containing protein 1</td>
<td>only in young</td>
<td>0.18</td>
<td>only in P15</td>
</tr>
<tr>
<td>Macrophage migration inhibitory factor</td>
<td>only in aged</td>
<td>only in HT</td>
<td>1.5</td>
</tr>
<tr>
<td>Major urinary protein 1</td>
<td>0.40</td>
<td>only in NT</td>
<td>0.50</td>
</tr>
<tr>
<td>Major vault protein</td>
<td>1.0</td>
<td>4.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Malate dehydrogenase, cytoplasmian</td>
<td>0.63</td>
<td>1.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Mast cell carboxypeptidase A</td>
<td>3.0</td>
<td>—</td>
<td>only in P15</td>
</tr>
<tr>
<td>Matrix-3</td>
<td>only in young</td>
<td>0.33</td>
<td>4.4</td>
</tr>
<tr>
<td>Matrix GlA protein</td>
<td>only in aged</td>
<td>only in HT</td>
<td>—</td>
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<tr>
<td>Medium-chain specific acyl-CoA dehydrogenase, mitoch.</td>
<td>0.75</td>
<td>0.85</td>
<td>only in P3</td>
</tr>
<tr>
<td>Metaxin-2</td>
<td>0.40</td>
<td>4.4</td>
<td>only in P15</td>
</tr>
<tr>
<td>Methionyl-tRNA synthetase, cytoplasmian</td>
<td>only in young</td>
<td>only in HT</td>
<td>2.3</td>
</tr>
<tr>
<td>Methylcrotonoyl-CoA carboxylase beta chain, mitoch.</td>
<td>only in young</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Methylcrotonoyl-CoA carboxylase subunit alpha, mitoch.</td>
<td>only in young</td>
<td>0.29</td>
<td>only in P15</td>
</tr>
<tr>
<td>Methylmalonyl-CoA mutase, mitoch.</td>
<td>only in young</td>
<td>0.50</td>
<td>only in P15</td>
</tr>
<tr>
<td>Microfibrillar-associated protein 5</td>
<td>12</td>
<td>4.0</td>
<td>only in P15</td>
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<tr>
<td>Microtubule-associated protein 4</td>
<td>only in young</td>
<td>only in HT</td>
<td>7.0</td>
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<tr>
<td>Mitoch. carrier homolog 2</td>
<td>0.31</td>
<td>1.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Mitoch. import receptor subunit TOM20 homolog</td>
<td>1.0</td>
<td>0.50</td>
<td>2.0</td>
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<tr>
<td>Mitoch. import receptor subunit TOM22 homolog</td>
<td>only in young</td>
<td>2.0</td>
<td>7.0</td>
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<tr>
<td>Mitoch. import receptor subunit TOM40 homolog</td>
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<td>Mitoch. inner membrane protein</td>
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<td>1.5</td>
<td>6.3</td>
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<tr>
<td>Monocarboxylate transporter 1</td>
<td>only in aged</td>
<td>1.0</td>
<td>only in P15</td>
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<td>Monofunctional C1-tetrahydrofolate synthase, mitoch.</td>
<td>—</td>
<td>—</td>
<td>0.33</td>
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<tr>
<td>Muscle-related coiled-coil protein</td>
<td>2.4</td>
<td>0.71</td>
<td>only in P15</td>
</tr>
<tr>
<td>Myosin binding protein C [cardiac form is cardioprotective][143]</td>
<td>1.4</td>
<td>2.1</td>
<td>2.3</td>
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<tr>
<td>Myosin light polypeptide 6</td>
<td>0.40</td>
<td>0.60</td>
<td>0.64</td>
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<tr>
<td>Myosin-1 [cardiomyopathy][144]</td>
<td>only in young</td>
<td>only in NT</td>
<td>1.4</td>
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<tr>
<td>Myosin-10</td>
<td>1.9</td>
<td>2.3</td>
<td>1.4</td>
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<td>Myosin-11</td>
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<td>2.0</td>
<td>0.78</td>
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<td>Myosin-14</td>
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<td>0.73</td>
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<td>Myosin-9</td>
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<td>Protein/Enzyme</td>
<td>Condition</td>
<td>Value 1</td>
<td>Value 2</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Myosin-Ib</td>
<td>only in young</td>
<td>only in HT</td>
<td>2.0</td>
</tr>
<tr>
<td>Myosin-Id</td>
<td>only in young</td>
<td>—</td>
<td>7.5</td>
</tr>
<tr>
<td>Myosin-Va</td>
<td>only in aged</td>
<td>—</td>
<td>0.43</td>
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<tr>
<td>Myosin-XVIIIa</td>
<td>0.50</td>
<td>0.67</td>
<td>only in P15</td>
</tr>
<tr>
<td>Myotilin [myofibrillar myopathy(145)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Myozenin-2</td>
<td>0.91</td>
<td>0.47</td>
<td>only in P15</td>
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<tr>
<td>NAD(P) transhydrogenase, mitoch.</td>
<td>80</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mitoch.</td>
<td>1.0</td>
<td>1.6</td>
<td>only in P3</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 11</td>
<td>only in young</td>
<td>3.5</td>
<td>only in P15</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12</td>
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<td>2.1</td>
<td>4.0</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13</td>
<td>only in young</td>
<td>3.4</td>
<td>2.0</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 2</td>
<td>0.60</td>
<td>3.1</td>
<td>only in P15</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 3</td>
<td>1.0</td>
<td>5.0</td>
<td>only in P15</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 5</td>
<td>2.5</td>
<td>only in HT</td>
<td>0.10</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 6</td>
<td>0</td>
<td>2.3</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 7</td>
<td>0.24</td>
<td>3.3</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8</td>
<td>0.13</td>
<td>4.6</td>
<td>—</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitoch.</td>
<td>0.13</td>
<td>2.6</td>
<td>—</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 10</td>
<td>0.80</td>
<td>24</td>
<td>only in P15</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11, mitoch.</td>
<td>0.25</td>
<td>9.5</td>
<td>only in P15</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 2, mitoch.</td>
<td>2.0</td>
<td>6.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 3</td>
<td>1.0</td>
<td>2.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 4</td>
<td>0.14</td>
<td>1.9</td>
<td>0.50</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 5, mitoch.</td>
<td>0.29</td>
<td>9.3</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 6</td>
<td>only in aged</td>
<td>18</td>
<td>only in P15</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 7</td>
<td>0.25</td>
<td>21</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8, mitoch.</td>
<td>0.42</td>
<td>12</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9</td>
<td>0.10</td>
<td>2.9</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] 1 subunit C2</td>
<td>only in young</td>
<td>8.5</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] flavoprotein 1, mitoch.</td>
<td>0.10</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] flavoprotein 2, mitoch.</td>
<td>0.43</td>
<td>9.9</td>
<td>0.50</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] flavoprotein 3, mitoch.</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitoch.</td>
<td>0.13</td>
<td>42</td>
<td>only in P15</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitoch.</td>
<td>0.64</td>
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<td>2.0</td>
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<td>NADH dehydrogenase [ubiquinone] iron-sulfur protein 4, mitoch.</td>
<td>only in young</td>
<td>4.8</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] iron-sulfur prot. 5 [Alzheimer, Down(146)]</td>
<td>only in young</td>
<td>8.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH dehydrogenase [ubiquinone] iron-sulfur prot. 6, mit. [Alzheimer,</td>
<td>only in young</td>
<td>21</td>
<td>only in P15</td>
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<tr>
<td>NADH dehydrogenase [ubiquinone] iron-sulfur protein 7, mitoch.</td>
<td>0.52</td>
<td>3.9</td>
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<td>NADH dehydrogenase [ubiquinone] iron-sulfur protein 8, mitoch.</td>
<td>0.14</td>
<td>7.1</td>
<td>only in P15</td>
</tr>
<tr>
<td>NADH-ubiquinone oxidoreductase 75 kDa subunit, mitoch.</td>
<td>0.21</td>
<td>4.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Protein Name</td>
<td>Expression Status</td>
<td>Value 1</td>
<td>Value 2</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>---------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>NADH-ubiquinone oxidoreductase chain 1 [Huntington disease(147)]</td>
<td>only in aged</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>NADH-ubiquinone oxidoreductase chn. 5 [Alzheimer disease, Down syndrome]</td>
<td>only in aged</td>
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<td></td>
</tr>
<tr>
<td>NADPH-cytochrome P450 reductase</td>
<td>only in aged</td>
<td></td>
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</tr>
<tr>
<td>Nascent polypeptide-associated complexes u. alpha, muscle-specific form</td>
<td>only in aged</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Nebulin-related-anchoring protein</td>
<td>only in aged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEDD8-conjugating enzyme Ubc12</td>
<td>only in aged</td>
<td></td>
<td></td>
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<tr>
<td>Nesprin-3</td>
<td>only in young</td>
<td>1.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Nestin [coronary heart disease(148)]</td>
<td>only in young</td>
<td>2.1</td>
<td>0.95</td>
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<tr>
<td>Neurofilament L chain [CSF biomarker of ALS(149)]</td>
<td>only in young</td>
<td>2.5</td>
<td>0.57</td>
</tr>
<tr>
<td>Nidogen-1 [Duchenne muscular dystrophy(150)]</td>
<td>only in aged</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Nidogen-2 [Ovarian Cancer(150)]</td>
<td>only in aged</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-POU domain-containing octamer-binding protein</td>
<td>only in aged</td>
<td>2.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Nuclear pore complex protein Nup214</td>
<td>only in aged</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Nuclear pore membrane glycoprotein 210</td>
<td>only in aged</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Nucleolar GTP-binding protein 1</td>
<td>only in aged</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Nucleolar transcription factor 1</td>
<td>only in aged</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Nucleolin</td>
<td>only in aged</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Nucleoside diphosphate kinase A</td>
<td>only in aged</td>
<td>1.7</td>
<td></td>
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<tr>
<td>Obscurin [cardiac myofibrillogenesis, hypertrophy(151)]</td>
<td>only in aged</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Optic atrophy 3 protein homolog</td>
<td>only in aged</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Ornithine aminotransferase, mitoch.</td>
<td>only in aged</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Palladin</td>
<td>only in aged</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Papilin</td>
<td>only in aged</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>PC4 and SFRS1-interacting protein</td>
<td>only in aged</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>PDZ and LIM domain protein 5</td>
<td>only in aged</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>PDZ and LIM domain protein 7</td>
<td>only in aged</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Peptide methionine sulfoxide reductase</td>
<td>only in aged</td>
<td>0.50</td>
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<tr>
<td>Perilipin-4</td>
<td>only in aged</td>
<td>2.0</td>
<td></td>
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<tr>
<td>Periostin [cardiac remodeling(152;153)]</td>
<td>only in aged</td>
<td>3.0</td>
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<tr>
<td>Peripherin [neuronal death(154)]</td>
<td>only in aged</td>
<td>2.3</td>
<td></td>
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<tr>
<td>Peroxiredoxin-2 [protection from dopaminergic neurodegeneration(155;156)]</td>
<td>only in young</td>
<td>0.83</td>
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<tr>
<td>Peroxiredoxin-4 [risk factor for type 2 diabetes, CVD, all-cause mortality]</td>
<td>only in young</td>
<td>1.0</td>
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<tr>
<td>Peroxiredoxin-5, mitoch. [Parkinson disease model(159)]</td>
<td>only in aged</td>
<td>0.91</td>
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<tr>
<td>Peroxiredoxin-6 [Parkinson disease model(160)]</td>
<td>only in aged</td>
<td>1.8</td>
<td></td>
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<tr>
<td>Peroxisomal multifunctional enzyme type 2</td>
<td>only in young</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Phenylalanyl-tRNA synthetase beta chain</td>
<td>only in aged</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Phosphate carrier protein, mitoch.</td>
<td>only in aged</td>
<td>0.34</td>
<td>0.53</td>
</tr>
<tr>
<td>Phosphatidylethanolamine-binding protein 1</td>
<td>only in aged</td>
<td>0.17</td>
<td>2.5</td>
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<tr>
<td>Phosphatidylinositol-binding clathrin assembly protein</td>
<td>only in aged</td>
<td>0.82</td>
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</tr>
<tr>
<td>Gene Name</td>
<td>Control Conditions</td>
<td>Sample Conditions</td>
<td>Ratio</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>--------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Phosphoenolpyruvate carboxykinase [GTP], mitoch.</td>
<td>only in aged</td>
<td>only in HT</td>
<td>0.46</td>
</tr>
<tr>
<td>Phosphoglucomutase-1</td>
<td>only in aged</td>
<td>only in P15</td>
<td>2.5</td>
</tr>
<tr>
<td>Phosphoglycerate kinase 1</td>
<td>3.6</td>
<td>0.50</td>
<td>1.1</td>
</tr>
<tr>
<td>Phosphoglycerate mutase 1</td>
<td>2.0</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Phosphoglycerate mutase 2</td>
<td>2.1</td>
<td>4.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Phospholipid hydroperoxide glutathione peroxidase, mitoch.</td>
<td>2.2</td>
<td>0.55</td>
<td>—</td>
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<tr>
<td>Phosphoserine aminotransferase</td>
<td>only in aged</td>
<td>only in HT</td>
<td>0.27</td>
</tr>
<tr>
<td>Pinin</td>
<td>1.0</td>
<td>—</td>
<td>3.0</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor 1 RNA-binding protein [Alzheimer disease(161)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>1.1</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>5.0</td>
<td>8.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>Plastin-3 [spinal muscular atrophy, Sezary syndrome(162;163)]</td>
<td>only in young</td>
<td>only in HT</td>
<td>2.7</td>
</tr>
<tr>
<td>Platelet glycoprotein 4</td>
<td>5.3</td>
<td>3.6</td>
<td>only in P15</td>
</tr>
<tr>
<td>Plectin-1 [Neuromuscular synapse integrity(164)]</td>
<td>1.6</td>
<td>0.61</td>
<td>2.0</td>
</tr>
<tr>
<td>Poly [ADP-ribose] polymerase 1</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.0</td>
</tr>
<tr>
<td>Poly(rC)-binding protein 2</td>
<td>1.3</td>
<td>0.59</td>
<td>1.9</td>
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<tr>
<td>Polyadenylate-binding protein 1</td>
<td>only in aged</td>
<td>—</td>
<td>0.59</td>
</tr>
<tr>
<td>Poly pyrimidine tract-binding protein 1</td>
<td>only in young</td>
<td>only in HT</td>
<td>2.7</td>
</tr>
<tr>
<td>Potassium channel subfamily K member 2</td>
<td>—</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Potassium-transporting ATPase alpha chain 2</td>
<td>only in young</td>
<td>0.58</td>
<td>only in P15</td>
</tr>
<tr>
<td>Pre-mRNA-processing factor 19</td>
<td>only in aged</td>
<td>—</td>
<td>5.0</td>
</tr>
<tr>
<td>Pre-mRNA-processing-splicing factor 8</td>
<td>only in aged</td>
<td>—</td>
<td>5.7</td>
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<tr>
<td>Presequence protease, mitoch.</td>
<td>only in aged</td>
<td>1.0</td>
<td>0.75</td>
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<tr>
<td>Probable ATP-dependent RNA helicase DDX5</td>
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<td>—</td>
<td>0.88</td>
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<tr>
<td>Probable glutathione peroxidase 8</td>
<td>—</td>
<td>only in HT</td>
<td>0.50</td>
</tr>
<tr>
<td>Procollagen C-endopeptidase enhancer 1</td>
<td>—</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Procollagen galactosyltransferase 1</td>
<td>only in aged</td>
<td>only in HT</td>
<td>0.29</td>
</tr>
<tr>
<td>Procollagen-lysine,2-oxoglutarate 5-dioxygenase 3</td>
<td>only in aged</td>
<td>only in HT</td>
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<tr>
<td>Profilin-1</td>
<td>1.0</td>
<td>only in NT</td>
<td>1.1</td>
</tr>
<tr>
<td>Programmed cell death 6-interacting protein</td>
<td>3.0</td>
<td>0.33</td>
<td>1.4</td>
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<tr>
<td>Prohibitin-1 [ischaemic cardiac injury(165;166)]</td>
<td>only in aged</td>
<td>0.89</td>
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<tr>
<td>Prohibitin-2 [ischaemic cardiac injury(167)]</td>
<td>14</td>
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<tr>
<td>Prolow-density lipoprotein receptor-related protein 1</td>
<td>only in aged</td>
<td>only in HT</td>
<td>8.5</td>
</tr>
<tr>
<td>Prolyl endopeptidase</td>
<td>only in aged</td>
<td>only in HT</td>
<td>3.7</td>
</tr>
<tr>
<td>Propionyl-CoA carboxylase alpha chain, mitoch.</td>
<td>only in aged</td>
<td>3.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>Propionyl-CoA carboxylase beta chain, mitoch.</td>
<td>only in aged</td>
<td>5.0</td>
<td>only in P15</td>
</tr>
<tr>
<td>Prostaglandin E synthase 3</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.0</td>
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<tr>
<td>Proteasomal ubiquitin receptor ADRM1</td>
<td>only in young</td>
<td>—</td>
<td>0.25</td>
</tr>
<tr>
<td>Proteasome subunit alpha type-1</td>
<td>1.3</td>
<td>1.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Proteasome subunit alpha type-5 [Alzheimer disease(168)]</td>
<td>only in aged</td>
<td>only in HT</td>
<td>3.5</td>
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<tr>
<td>Proteasome subunit alpha type-6 [tauopathies &amp; synucleinopathies(169)]</td>
<td>3.0</td>
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<td>2.0</td>
</tr>
<tr>
<td>Protein Name</td>
<td>Value</td>
<td>Value</td>
<td>Value</td>
</tr>
<tr>
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<tr>
<td>Proteasome subunit alpha type-7</td>
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<td>Proteasome subunit beta type-1</td>
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<tr>
<td>Proteasome subunit beta type-2</td>
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<td>4.0</td>
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<tr>
<td>Proteasome subunit beta type-3</td>
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<tr>
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<td>Proteasome subunit beta type-5</td>
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<td>1.4</td>
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</tr>
<tr>
<td>Proteasome subunit beta type-7 [Alzheimer disease (168)]</td>
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<tr>
<td>Proteasome subunit beta type-8 [ autoinflammatory disorder(170)]</td>
<td>only in aged</td>
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<tr>
<td>[Protein ADP-ribosylarginine] hydrolase-like protein 1</td>
<td>only in young</td>
<td>0.40</td>
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<tr>
<td>Protein disulfide-isomerase</td>
<td>only in young</td>
<td>only in HT</td>
<td>1.2</td>
</tr>
<tr>
<td>Protein disulfide-isomerase A3</td>
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<td>1.3</td>
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<tr>
<td>Protein DJ-1</td>
<td>0.75</td>
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<td>only in NT</td>
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<tr>
<td>Protein FAM54B</td>
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<td>0.20</td>
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<tr>
<td>Protein flightless-1 homolog</td>
<td>only in young</td>
<td>only in HT</td>
<td>3.3</td>
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<tr>
<td>Protein NipSnap homolog 2</td>
<td>0.27</td>
<td>0.46</td>
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<tr>
<td>Protein RRP5 homolog</td>
<td>1.0</td>
<td>2.0</td>
<td>1.5</td>
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<tr>
<td>Protein S100-A10</td>
<td>only in aged</td>
<td>only in HT</td>
<td>1.4</td>
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<tr>
<td>Protein S100-A6</td>
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<td>1.0</td>
<td>7.5</td>
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<tr>
<td>Protein unc-45 homolog B</td>
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<tr>
<td>Protein-cysteine N-palmitoyltransferase HHAT-like protein</td>
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<td>1.7</td>
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<tr>
<td>Protein-glutamine gamma-glutamyltransferase 2</td>
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<td>Pumilio domain-containing protein KIAA0020</td>
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<td>only in HT</td>
<td>2.0</td>
</tr>
<tr>
<td>Purine nucleoside phosphorlyase</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Putative ATP-dependent RNA helicase PI10</td>
<td>1.0</td>
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<td>—</td>
</tr>
<tr>
<td>Putative ribosomal RNA methyltransferase NOP2</td>
<td>only in aged</td>
<td>only in HT</td>
<td>2.3</td>
</tr>
<tr>
<td>Putative RNA-binding protein 3</td>
<td>only in aged</td>
<td>only in HT</td>
<td>5.7</td>
</tr>
<tr>
<td>Pyridoxal kinase</td>
<td>only in aged</td>
<td>only in HT</td>
<td>only in P15</td>
</tr>
<tr>
<td>Pyrroline-5-carboxylate reductase 2</td>
<td>only in young</td>
<td>only in HT</td>
<td>2.0</td>
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<td>Rab GDP dissociation inhibitor beta</td>
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<td>Radixin</td>
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<td>Ras-related C3 botulinum toxin substrate 1</td>
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<td>Ras-related C3 botulinum toxin substrate 2</td>
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<td>Regulator of nonsense transcripts 1</td>
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<td>Rho GDP-dissociation inhibitor 2</td>
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<td>Rho-associated protein kinase 2</td>
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<td>Ribosomal RNA processing protein 1 homolog A</td>
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<td>Ribosome biogenesis protein BOP1</td>
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<td>RNA-binding protein FUS</td>
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<td>RNA-binding protein Raly</td>
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<td>Sarcalumenin [age-related cardiac dysfunction(171;172)]</td>
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<td>Sarcomplasmic/endoplasmic reticulum calcium ATPase 1 [CVD(173)]</td>
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<td>Septin-7</td>
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<td>Serine/threonine-protein kinase DCLK1</td>
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<td>Ser/thr-protein phosphatase PGAM5, mitoch. [Parkinsonian diseases(179)]</td>
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<td>Serine/threonine-protein phosphatase PP1-alpha catalytic subunit [Cancer(180)]</td>
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<td>Serine/threonine-protein phosphatase PP1-gamma catalytic subunit</td>
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<td>Serotransferrin [valvular heart disease biomarkers(181)]</td>
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<td>Serpin H1</td>
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<td>Serum albumin</td>
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<td>Serum deprivation-response protein</td>
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<td>Seryl-tRNA synthetase, cytoplasmic</td>
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<tr>
<td>SET and MYND domain-containing protein 1 [Cancer and cardiac dysfunc(182)]</td>
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<td>SH3 domain-binding glutamic acid-rich-like protein 3</td>
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<td>only in HT 2.0</td>
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<tr>
<td>Short-chain specific acyl-CoA dehydrogenase, mitoch.</td>
<td>1.8</td>
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</table>

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Note: The table represents the expression levels and patterns of various proteins. The expression levels are given in arbitrary units, and the patterns indicate whether the expression is only in aged, only in NT, only in P15, or in young only in HT.
<table>
<thead>
<tr>
<th>Protein Name</th>
<th>Regulation</th>
<th>Description</th>
<th>Fold Change</th>
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<tbody>
<tr>
<td>Signal peptidase complex catalytic subunit SEC11A</td>
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<td>Small nuclear ribonucleoprotein E</td>
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<td>Small nuclear ribonucleoprotein Sm D2</td>
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<tr>
<td>Small nuclear ribonucleoprotein Sm D3</td>
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<td>— 1.8</td>
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<tr>
<td>Small nuclear ribonucleoprotein-associated protein B</td>
<td>only in aged</td>
<td>only in HT only in P15</td>
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<tr>
<td>S-methyl-5'-thioadenosine phosphorylase</td>
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<td>only in HT 3.0</td>
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<tr>
<td>Sodium/potassium-transporting ATPase subunit alpha-1</td>
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<td>Sorbin and SH3 domain-containing protein 1</td>
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<td>0.84 11</td>
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<td>Spectrin beta chain, brain 1 [cardiac development(184)]</td>
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<td>1.2 12</td>
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<td>Spectrin beta chain, erythrocyte</td>
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<td>Splicing factor 3B subunit 1</td>
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<td>only in HT 2.0</td>
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<td>only in HT 4.0</td>
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<td>Splicing factor, proline- and glutamine-rich</td>
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<td>only in HT 7.8</td>
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<td>Src substrate cortactin</td>
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<td>Stress-70 protein, mitoch. [aging, cardiovascular disease(185)]</td>
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<td>0.50 0.80</td>
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<td>Striated muscle-specific serine/threonine-protein kinase</td>
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<td>Structural maintenance of chromosomes flexible hinge domain protein 1</td>
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<td>Structural maintenance of chromosomes protein 1A</td>
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<td>1.4 3.0</td>
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<td>Succinate dehydrogenase [ubiquinone] cytochrome b small s.u., mitoch.</td>
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<td>1.3 1.8</td>
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<td>0.57 0.14</td>
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<td>0.31 1.0</td>
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<td>only in NT only in P3</td>
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<td>Expression in NT</td>
<td>Expression in P3</td>
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<td>only in P3</td>
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<td>SUN domain-containing protein 1</td>
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<td>only in HT</td>
<td>only in P15</td>
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<td>SUN domain-containing protein 2</td>
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<td>Superoxide dismutase [Cu-Zn] [age-related cognitive decline(186)]</td>
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<td>only in NT</td>
<td>only in P3</td>
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<td>SUN domain-containing protein 1</td>
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<tr>
<td>SUN domain-containing protein 2</td>
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<td>Synaptarin-II-like protein [cardiac &amp; skeletal muscle function(191)]</td>
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<td>Thioredoxin reductase 1, cytoplasmic</td>
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<td>Thymosin beta-4 [cardioprotection(194;195)]</td>
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<td>Transmembrane protein 11</td>
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<td>Protein Name</td>
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<td>Value 2</td>
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<td>Transmembrane protein 65</td>
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<td>Transportin-1</td>
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<td>Transthyretin [transthyretin cardiac amyloidosis(197;198)]</td>
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<td>only in HT</td>
<td>only in P15</td>
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<tr>
<td>Trifunctional enzyme subunit alpha, mitoch. [Alzheimer disease, diabetes(199)]</td>
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<td>Trifunctional enzyme subunit beta, mitoch.</td>
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<td>Tripartite motif-containing protein 72</td>
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<td>Tropomyosin alpha-4 chain [breast cancer(200)]</td>
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<td>Tubulin alpha-8 chain</td>
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<td>Tyrosyl-tRNA synthetase, cytoplasmic</td>
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<td>Ubiquitin carboxyl-terminal hydrolase 5 [Alzheimer &amp; other tauopathies(201)]</td>
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<td>only in HT</td>
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<td>V-type proton ATPase catalytic subunit A</td>
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<td>V-type proton ATPase subunit d 1</td>
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<td>Wolframin [diabetes, neurodegeneration in Wolfram syndrome(217;218)]</td>
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<td>only in HT</td>
<td>only in P15</td>
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<tr>
<td>Xin actin-binding repeat-containing protein 1 [skeletal myopathies(219)]</td>
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<tr>
<td>Xin actin-binding repeat-containing protein 2 [myopathies, filaminopathies(220)]</td>
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Table S3. GO Analysis: Enrichment of functional annotation terms for proteins differentially represented in cardiac aggregates with aging, aligned with results for hypertension and myofibroblast senescence in vitro

GO terms are listed if the Benjamini-corrected FDR was <0.05 for aging. Corresponding fold changes and FDR values are also shown for hypertension and in vitro fibroblast aging, if reported by DAVID.

*These proteins are in both the UP and DOWN lists; i.e., separate subsets of proteins in these GO categories increased and decreased with cardiac aging. Combining both UP and DOWN lists for “contractile fiber” gives a total of 22 proteins, with a combined FDR <E−15; the total for “proteasome complex” was 12 proteins, FDR<2E−11; methylation totaled 17 proteins, FDR<2E−6; “phosphoprotein” totaled 140 proteins, FDR<2E−9; UBL totaled 21 proteins, FDR>0.05.

†These proteins increased with hypertension, but decreased with cardiac aging.

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<th>Fibroblast Aging</th>
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<td>*Proteasome complex [subunit α/β]</td>
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<th>FDR</th>
<th>Fold Δ</th>
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### C. GO terms DOWN with Cardiac Aging

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### D. GO Terms DOWN with Hypertension but not Cardiac Aging

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