



PROJECT FINAL REPORT

Grant Agreement number: 277936

Project acronym: META-PREDICT

Project title: Developing predictors of the health benefits of exercise for individuals

Funding Scheme: [HEALTH.2011.2.4.3-3 HEALTH.2011.2.4.2-2 HEALTH] Molecular and physiological effects of lifestyle factors on diabetes/obesity. Evaluation and validation studies of clinically useful biomarkers in prevention and management of cardiovascular disease Health.

Period covered: from 01/12/2011 to 01/07/2016 (incl. extension 6 months)

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4.1 Final publishable summary report

THIS FILE CONTAINS THE FIGURES AND TABLES ONLY. These belong to the text submitted online

4.1a - Executive Summary

4.1b - A summary description of project context and objectives

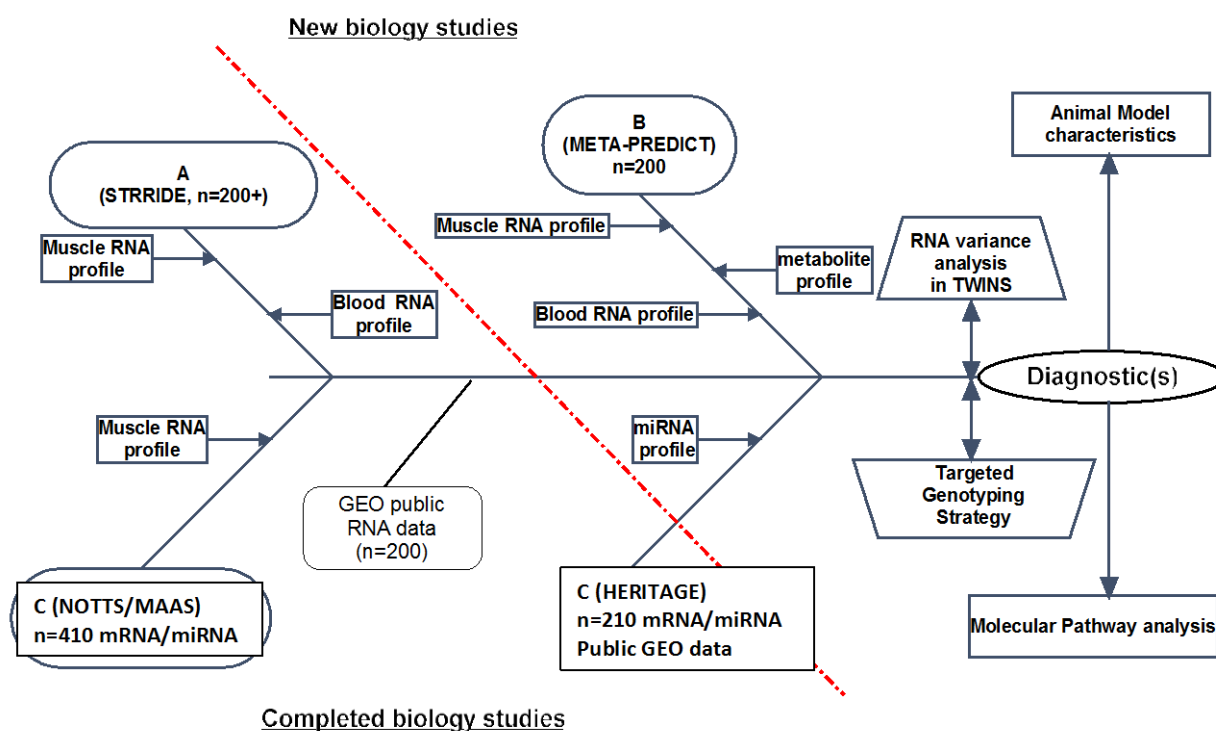


Figure 1. A high-level overview of the META-PREDICT. We have independent exercise life-style modification programs (A-D) with common clinical end-points that feed into a 'predictor' pipeline where we generate diagnostic screens from RNA, mDNA and metabolites. This will lead to personalised diagnostics, greater understanding of the underlying biology, and biomarkers for validating a novel drug screening in vivo model. Studies A and part of D have existing RNA gene-chip profiles; Study C has miRNA and mRNA deposited in the public domain (GEO). Study B will be the largest study of time-efficient cycle-sprint training in at-risk (metabolic disease) subjects studied using HTA 2.0 RNA, miRNA and mDNA chips.

4.1c - A description of the main S&T results/foreground

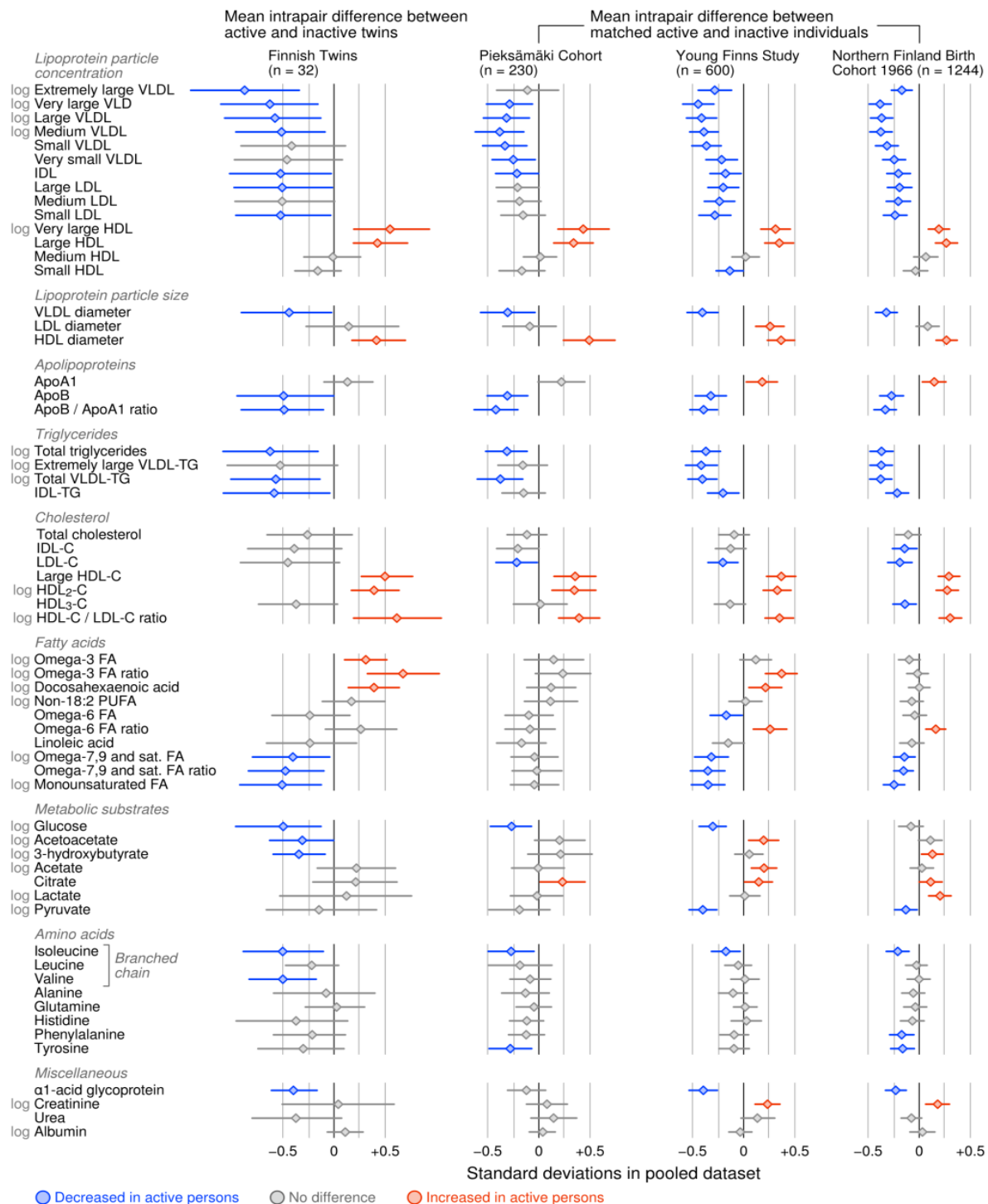


Figure 2. Metabolomics analyses in a smaller cohort of Twins with significant difference in level of physical activity (left) which was confirmed in larger cohorts of matched individuals with high and low levels of physical activity. From original publication (16).

Table 1. Interval-training induced concentration differences between HRT and LRT female rats. The concentrations for the metabolites are given as mean±SD in μM. TRP:tryptophane.

Metabolite(μM)	FemaleHRT		FemaleLRT		p-value	FDR
	PRE	POST	PRE	POST		
Lauroylcarnitine	0.04±0.02	0.02±0.01	0.03±0.02	0.02±0.01	3.97E-09	1.71E-07
Stearoylcarnitine	0.11±0.10	0.05±0.04	0.07±0.04	0.04±0.02	5.30E-08	1.14E-06
Octanoylcarnitine	0.02±0.01	0.02±0.01	0.02±0.01	0.03±0.02	1.23E-07	1.77E-06
Myristoylcarnitine	0.12±0.09	0.04±0.03	0.10±0.07	0.04±0.02	7.69E-07	8.26E-06
Hexanoylcarnitine	0.05±0.02	0.05±0.02	0.05±0.03	0.09±0.06	1.27E-05	0.0001094
TRP	107.4±9.7	98.8±9.5	102.5±15.1	98.4±13.1	0.0016521	0.01184

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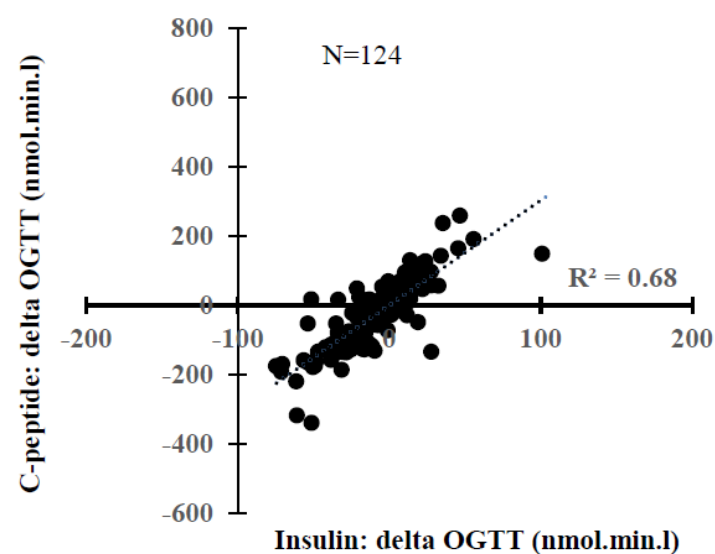
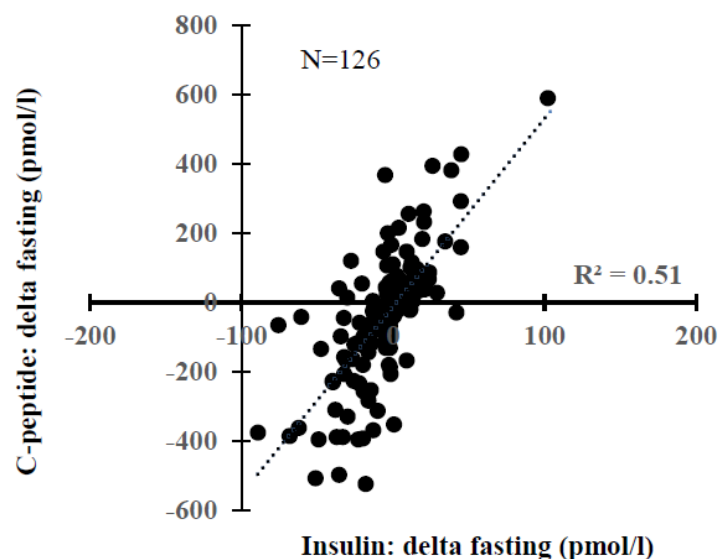


Figure 3: Human Studies - Presentation of the linear relationship between changes in plasma insulin and plasma C-peptide concentrations following 6 weeks of '5-by-1' HIT protocol. Oral glucose tolerance test (OGTT). Value is based on Pearson correlation coefficients (coefficient of determination).

Table 2. Subject characteristics for the HIT study

	Non-exercise (n=13)	'7-by-1' HIT (n=40)	'5-by-1' HIT (n=137)
Gender (men/women)	4 / 9	20 / 20	63 / 74
Age (y)	25 (20-51)	38 (20-53)	38 (18-51)
Height (m)	1.66 (1.52-1.81)	1.71 (1.53-1.94)	1.72 (1.51-2.01)
BMI (kg·m ⁻²)	32.7 (27.3-41.4)	29.8 (27.0-45.5)	31.2 (26.5-48.1)
Fasting glucose (mmol·L ⁻¹)	4.6 (4.0-5.2)	4.5 (3.8-5.4)	4.6 (3.3-5.6)
2hr OGTT glucose (mmol·L ⁻¹)	6.3 (5.2-9.4)	6.5 (4.2-10.5)	6.8 (3.7-10.1)
IPAQ Score	248 (160-1188)	382 (73-594)	330 (0-597)

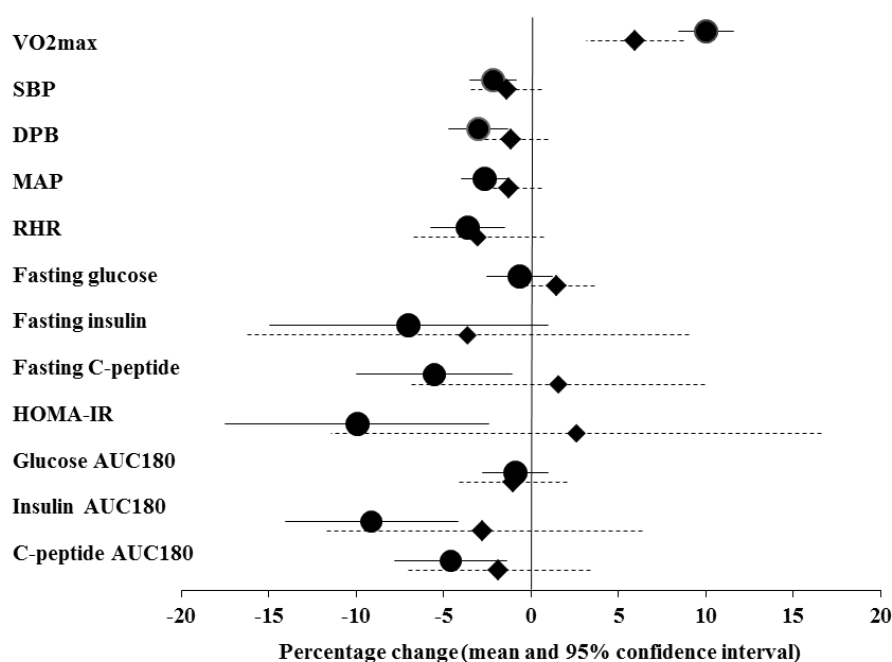


Figure 4: Comparison of the efficacy of 6 weeks of the '5-by-1' HIT high intensity cycle based exercise training protocol (black circles) with the less effective '7-by-1' HIT (black diamonds) protocol in obese or over-weight adults. The values are presented as mean $\pm$ 95% CI for the main training responses. AUC: area under the curve during oral glucose tolerance testing (180 min); SBP: Supine systolic blood pressure; DPB: Supine diastolic blood pressure; MAP: Supine mean arterial pressure; RHR: resting heart rate.

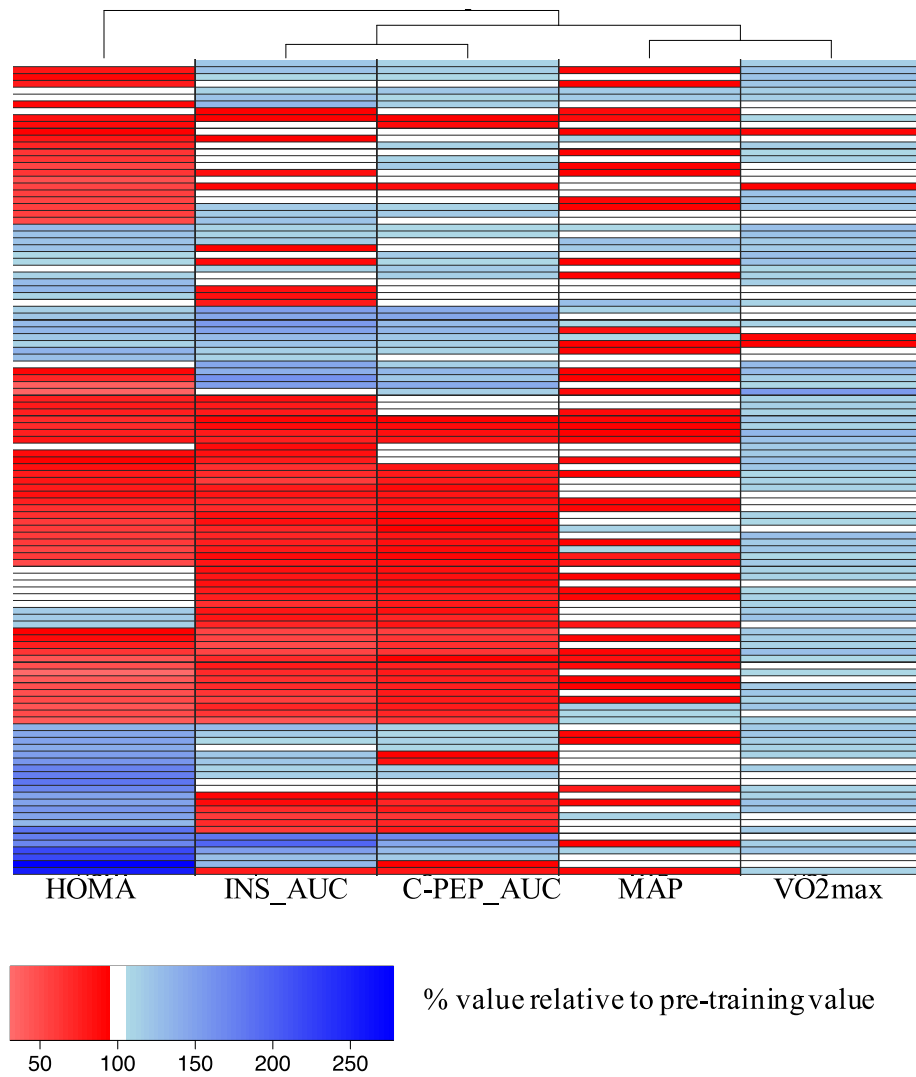


Figure 5: Heat-map representation of the individual responses to exercise training for 5 variables following ‘5-by-1’ HIT ($\dot{V}O_{2max}$, MAP, Oral glucose tolerance test (OGTT) Insulin AUC_{180} and HOMA-IR). It can be observed that each subject demonstrates a differential response to the 5 clinical parameters. Some subjects improve all five, most improve 2 or 3 while some do not improve any of these health biomarkers.

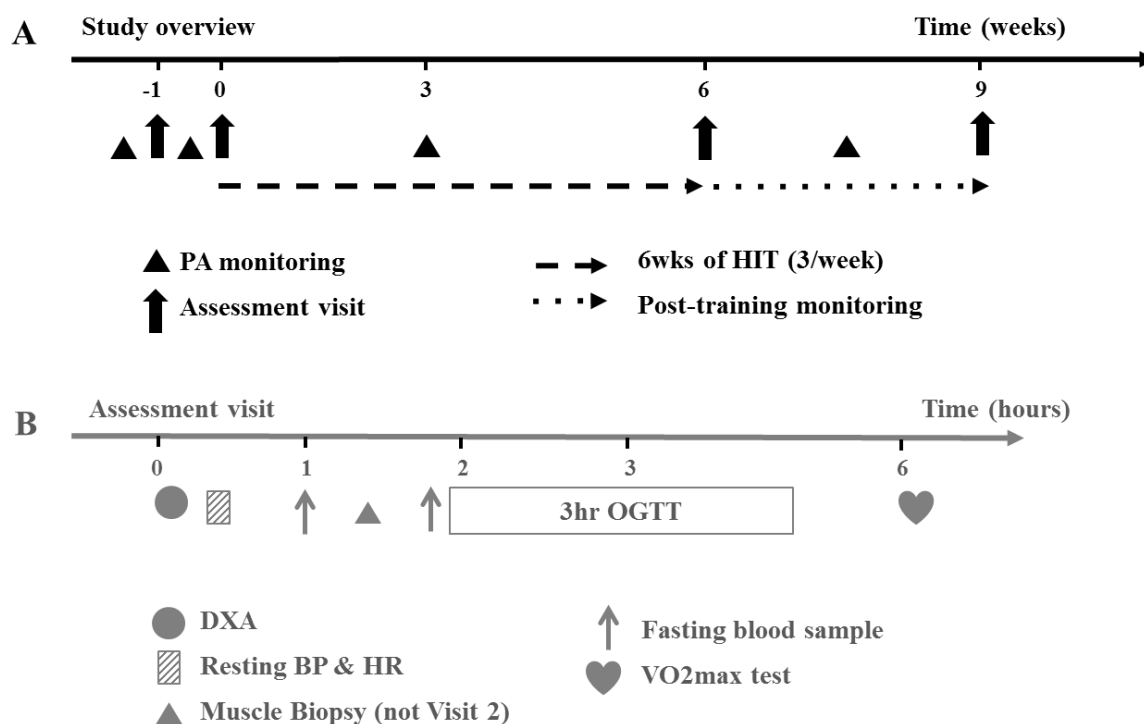


Figure 6. META-PREDICT HIT study design. Six weeks of supervised HIT was preceded by two study visits (baseline measurements, one week apart) and followed by another two study visits, post-training (~3 days after final session) and post-training monitoring (3 weeks after the final session). After an overnight fast, a DXA scan was followed by two fasted blood samples and a muscle biopsy, a standard 75-g OGTT, a standardised meal and a $\dot{V}O_2$ max-test. The DXA scan and muscle biopsies were not performed during Study visit 2.

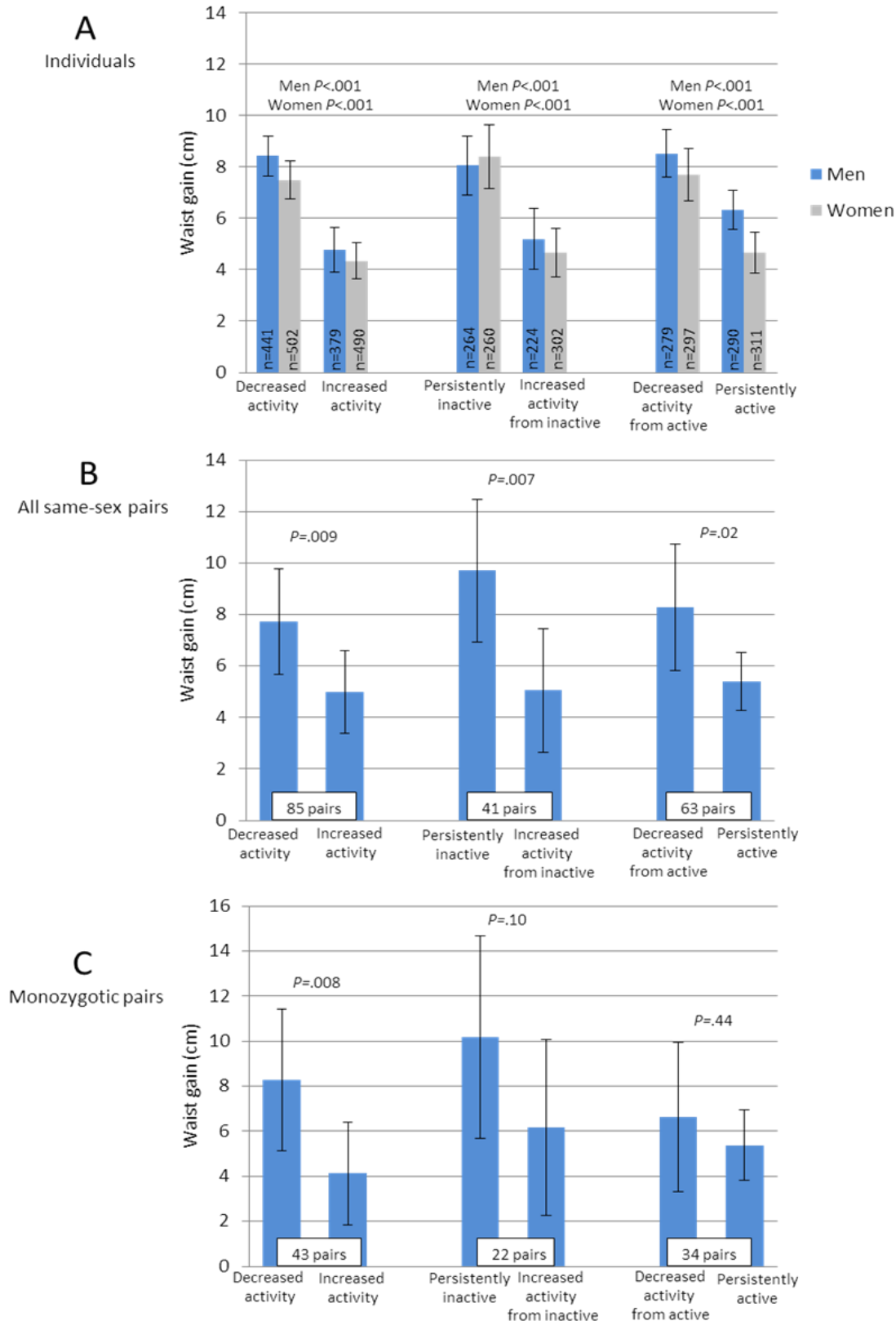


Figure 7. Differences in waist gain (cm, mean and 95%CI) during follow-up (decreased activity: changed from upper third to a lower one; increased activity: changed from a lower third to upper one). (A) Sex-specific differences among individuals taking into account clustered observation of twin pairs. (B) Pairwise difference among leisure-time physical activity discordant same-sex twin pairs. (C) Pairwise differences among leisure-time physical activity discordant monozygotic twin pairs (from (28)).

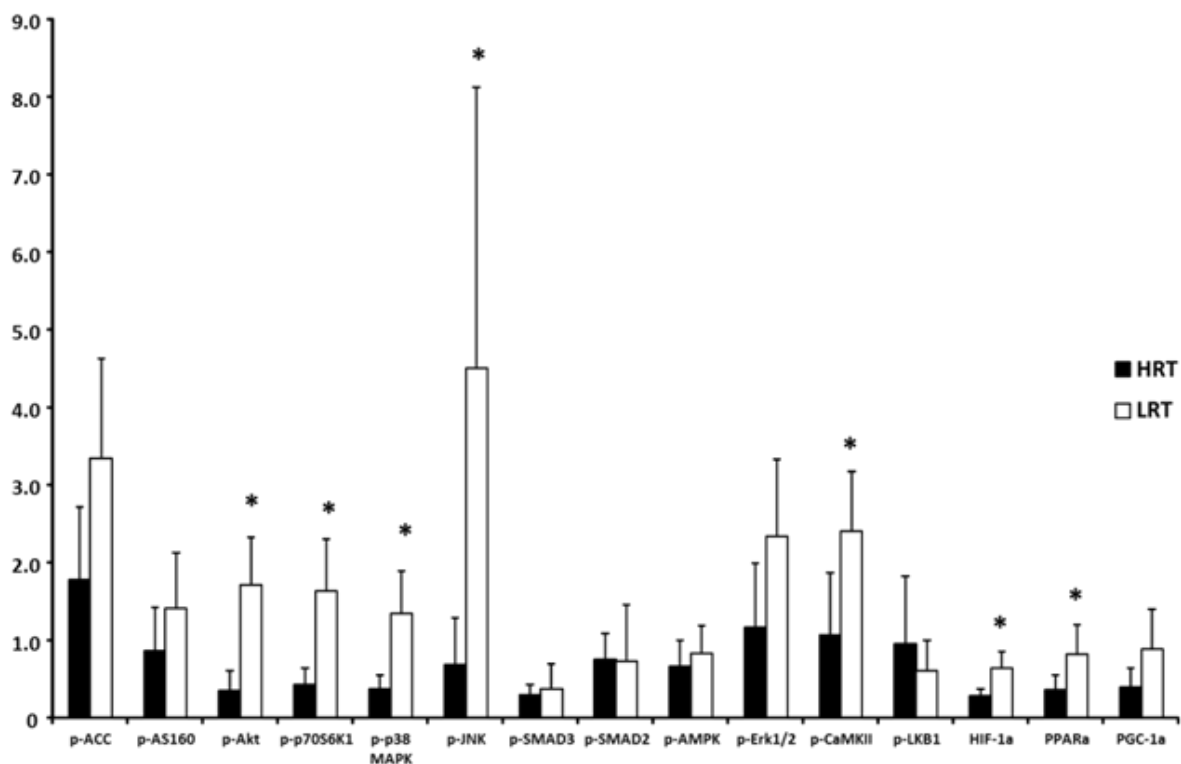


Figure 8. Content of selected signaling proteins [mean (SD)] in skeletal muscle (m.gastrocnemius) of high and low responder rats following acute high intensity exercise. * = statistically significant difference between the rat lines.

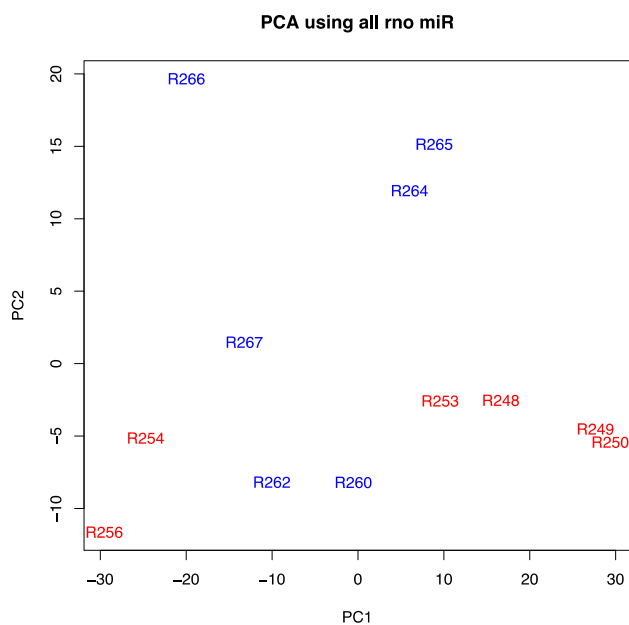
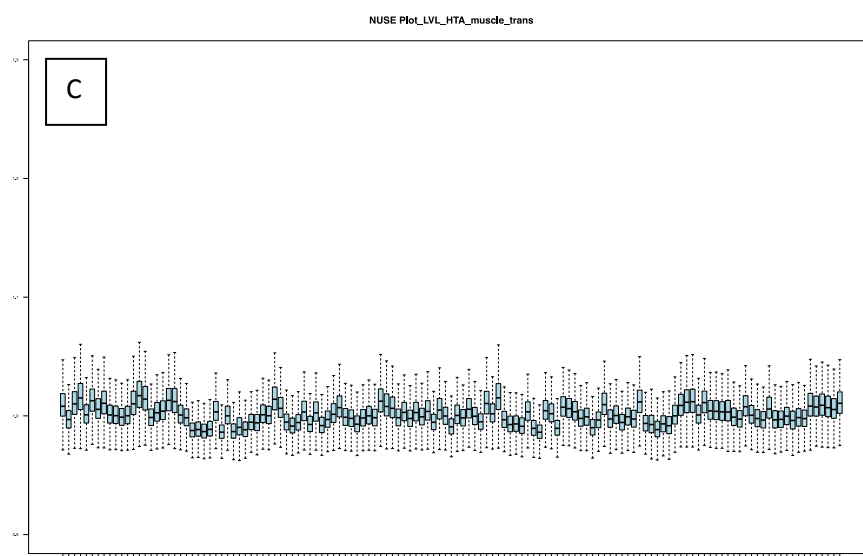
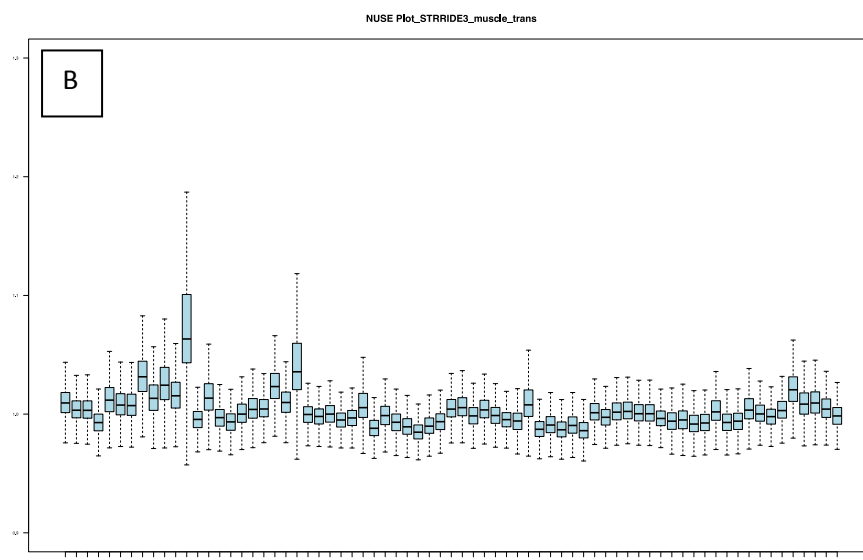
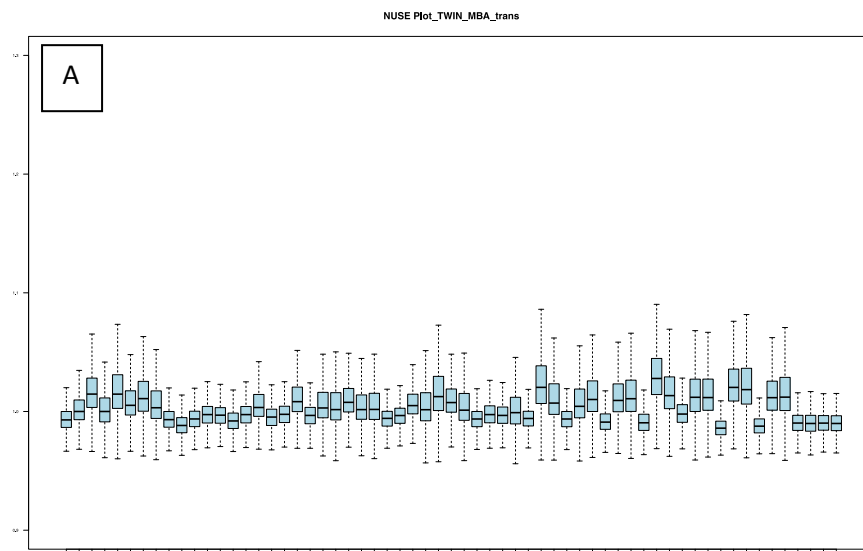


Figure 9. The impact WP5 D5.3 experiment on Rat miRNA PCA (Affymetrix)



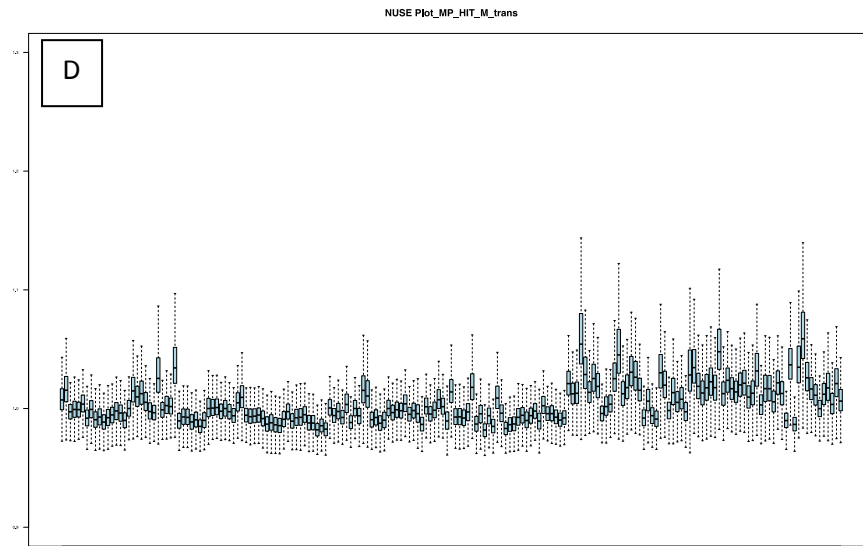
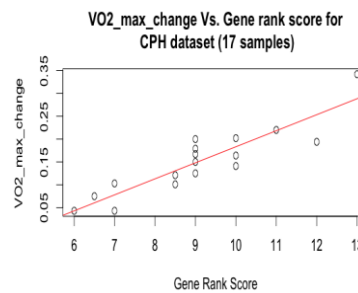
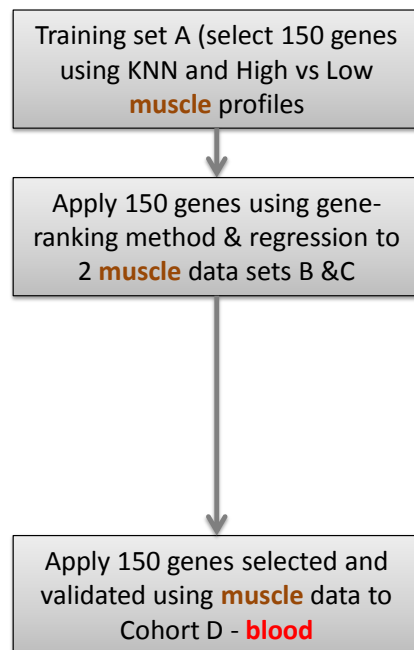
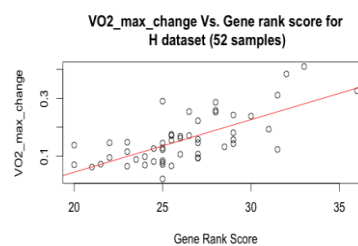


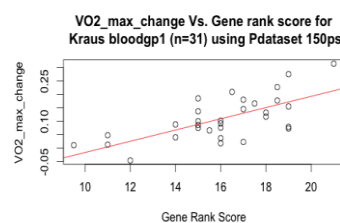
Figure 12. NUSE plots for muscle samples from A) the TWINN study, B) STRIDDE III, C) LVL Maastricht study and D) HIT study.



$R^2=0.806$
 $p\text{-value}=1.01E-06$



$R^2=0.483$
 $p\text{-value}=1.11E-08$



Baseline Blood Profile
in subjects that did AT.
 $R^2=0.461$
 $p\text{value}=2.65E-05$

Figure 13. Using new (WP8) DUKE blood chip data (n=124 baseline from 289) we took the muscle based aerobic predictor signature genes and attempt to reproduce this classifier from the blood RNA profile.

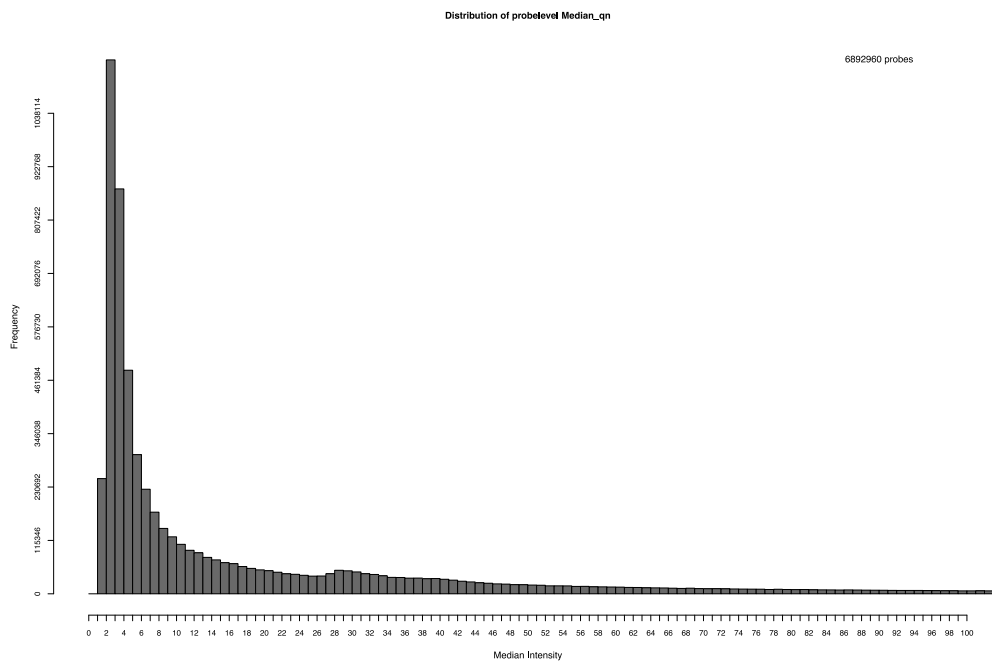


Figure 14. Demonstrating the large peak of background probe signal seen in the ‘raw’ HTA 2.0 chip data in MP muscle samples.

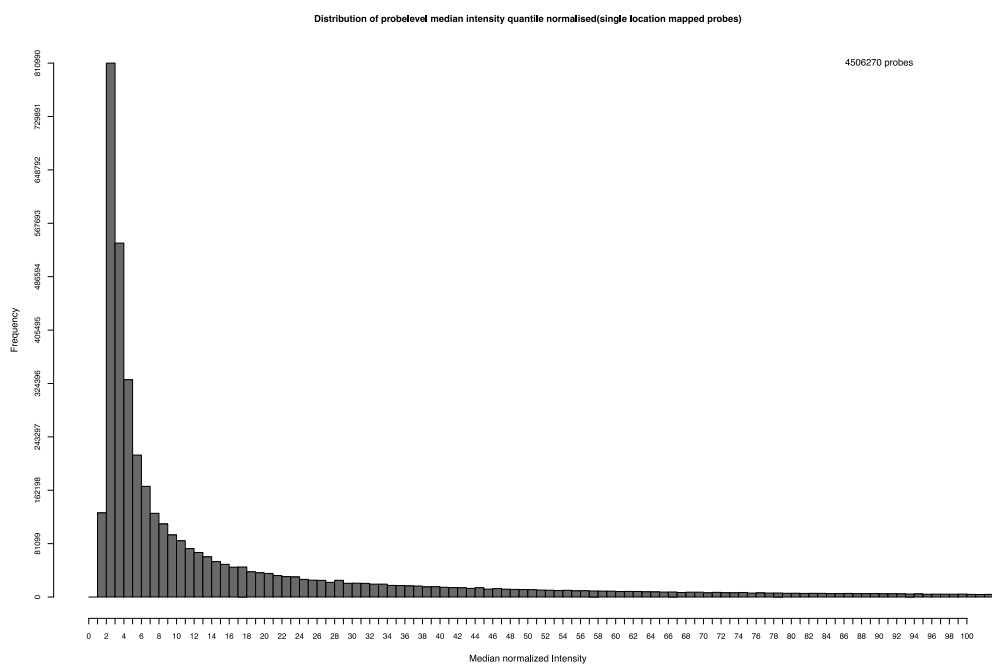


Figure 15. Demonstrating the impact of re-alignment of the original HTA 2.0 probes to the latest genome sequence - ~2.4Million probes are removed.

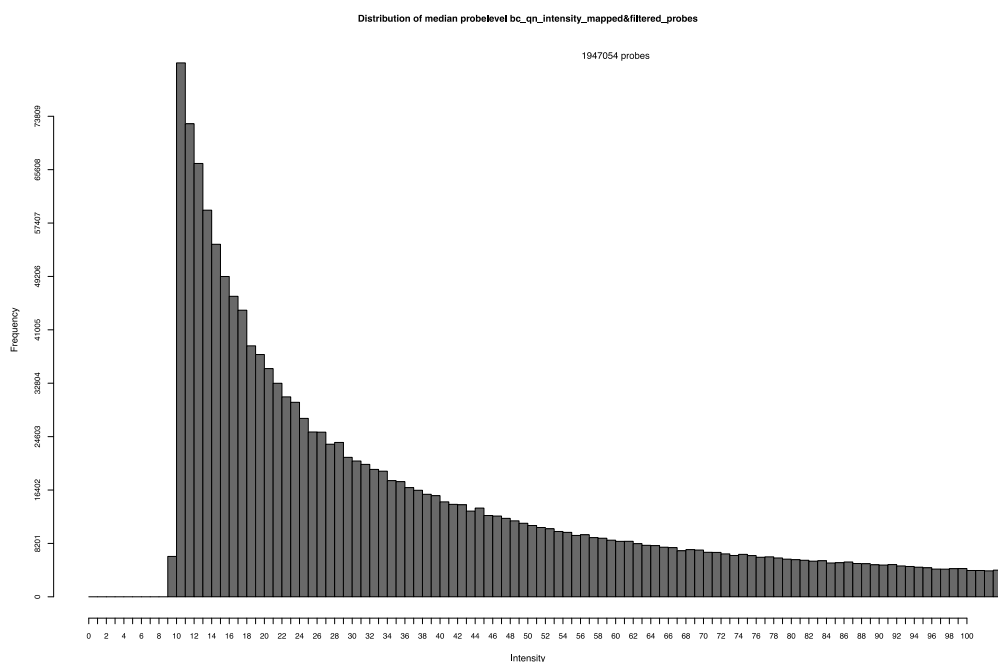


Figure 16. Demonstrating the impact of processing the filtered HTA 2.0 probes to reflect the probes expressed in a tissue specific manner - ~2.3Million probes are removed.

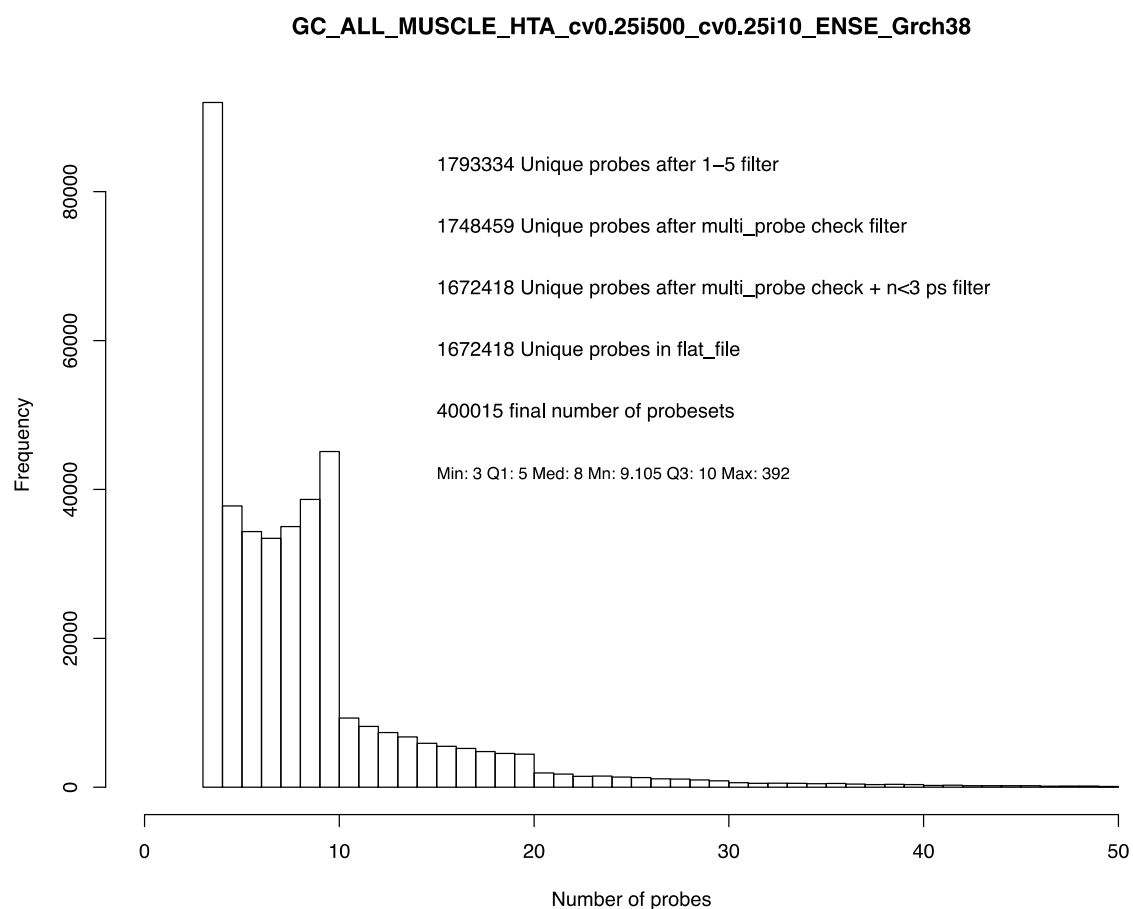


Figure 17. A muscle specific HTA 2.0 ‘probe’ map that is then assembled into probe-sets to detect individual exons. Only exons (probesets) with $n=3$ probes or more, aligned to 1 place in genome and containing probes above background signal are included.

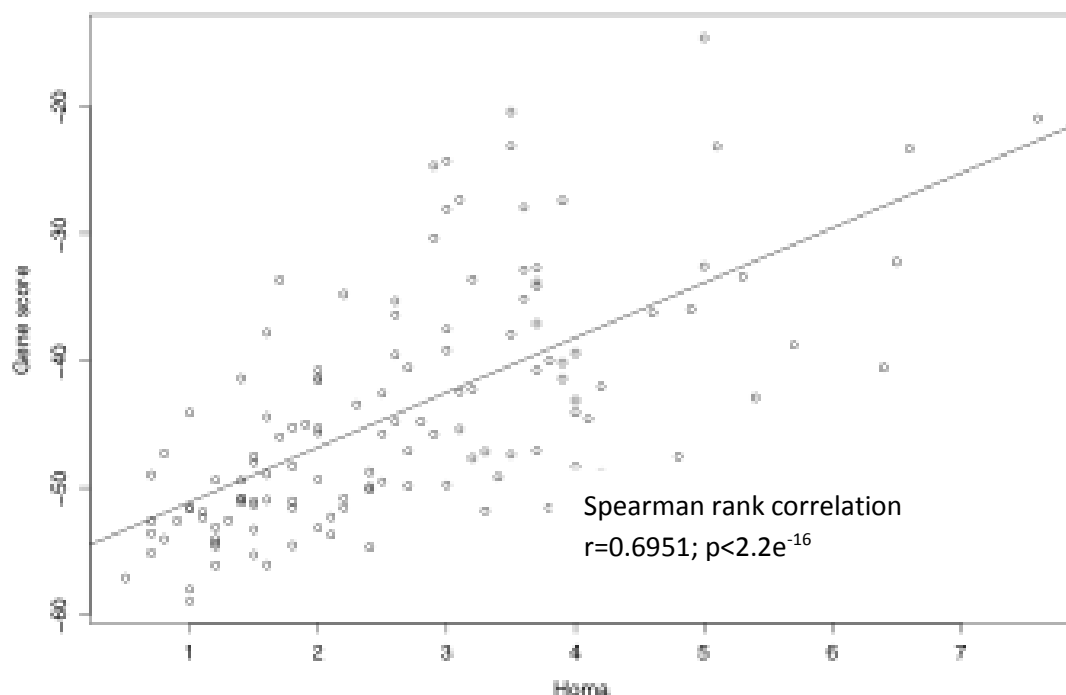


Figure 18. An example of a proto-type blood RNA versus HOMA linear model (Using STRRIDE II blood data). This is a simple Knn + Ranking model was generated prior to custom CDF methodology and will be further developed to replicate across cohorts using the new linear modeling code and CDFS.

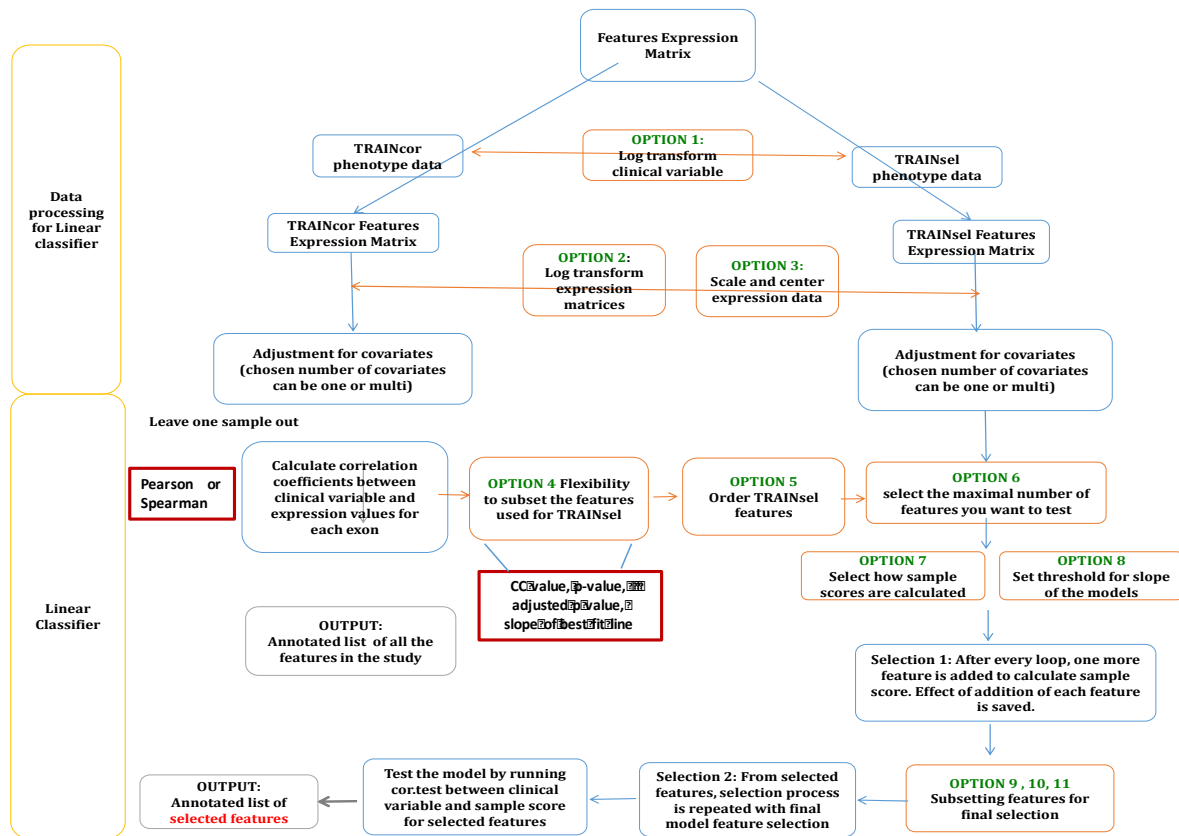


Figure 19. XRGenomics computational strategy for linear code

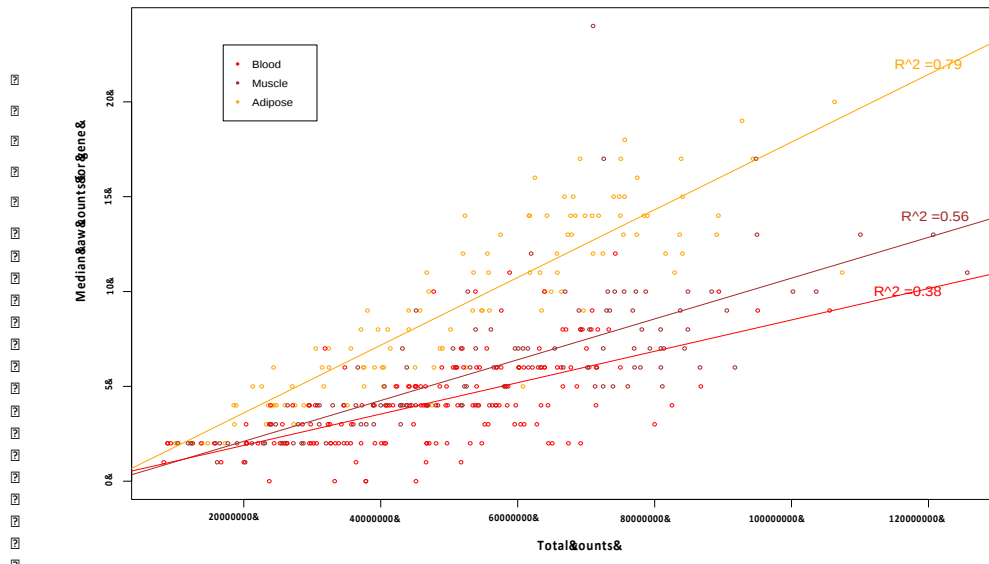


Figure 20. RNA sequencing not able to produce a strongly linear signal for lower expressed human tissue genes (especially muscle and blood).

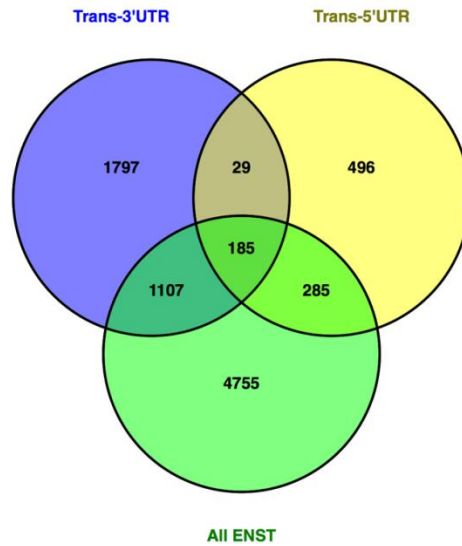


Figure 21. Full-Transcript, 3'UTR-transcript and 5'UTR-transcript regulation in response to 6 weeks of 5by1 HIT (WP3) in the skeletal muscle of subjects that demonstrate a gain in aerobic capacity (FDR 10%, FC>1.2)

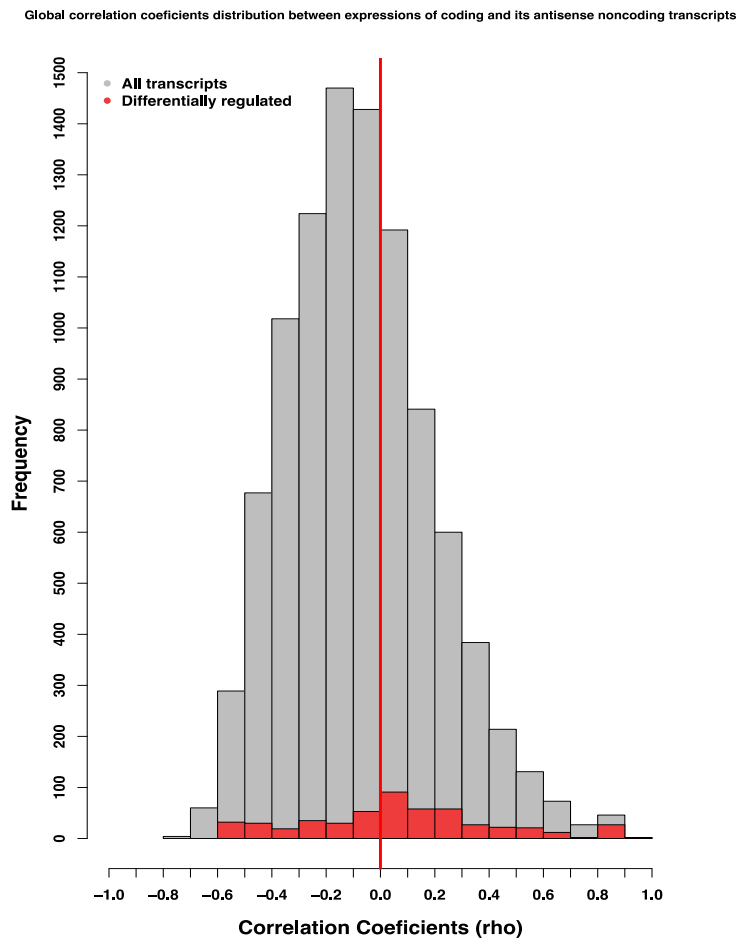


Figure 22. Global correlation between lncRNA and CIS protein coding genes in human skeletal muscle (and HIT exercise regulated genes in red).

Analysis: code vs noncode corr genes – 2016–08–06 04:42 PM

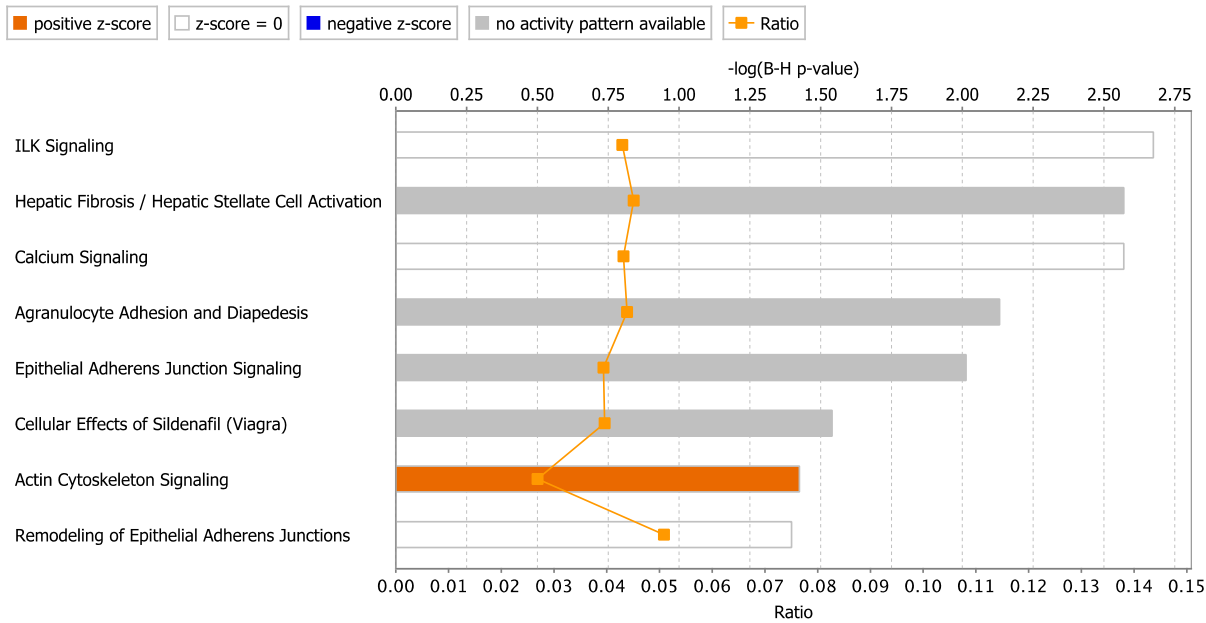


Figure 23. Up-stream regulators associated with the protein-coding genes that are co-regulated with the lncRNA exercise responsive genes in subjects that demonstrate a robust improvement in aerobic capacity

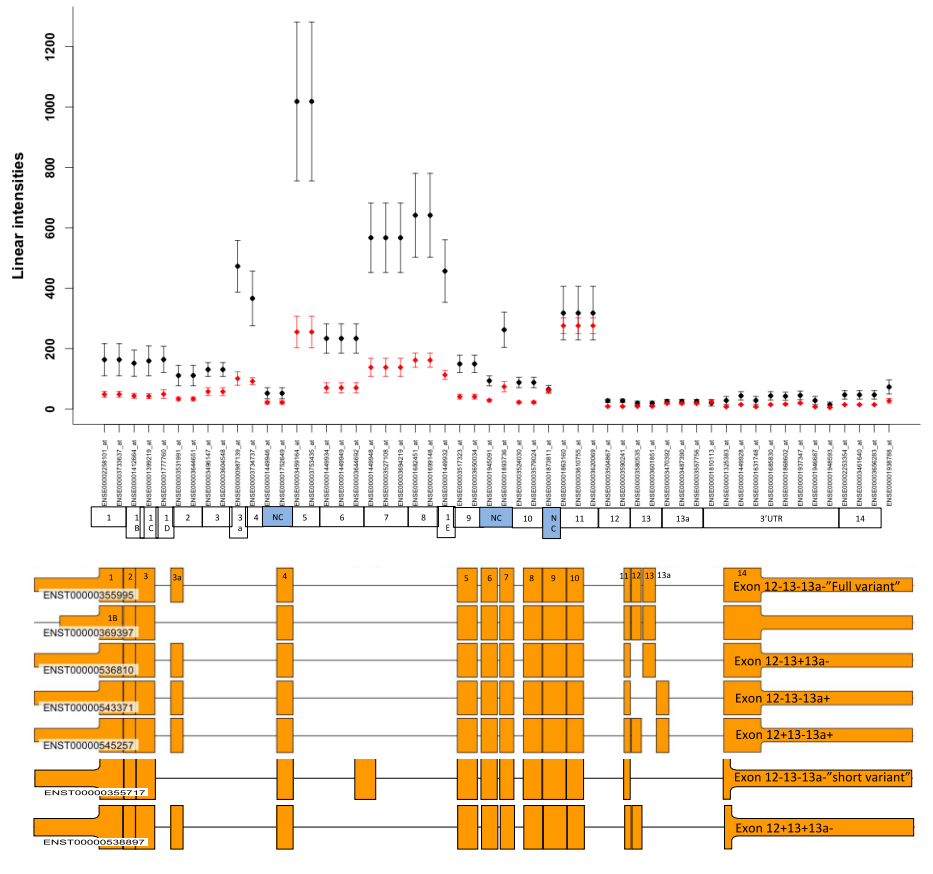


Figure 24. Probe-sets for TCF7L2 in muscle and adipose (WP5).

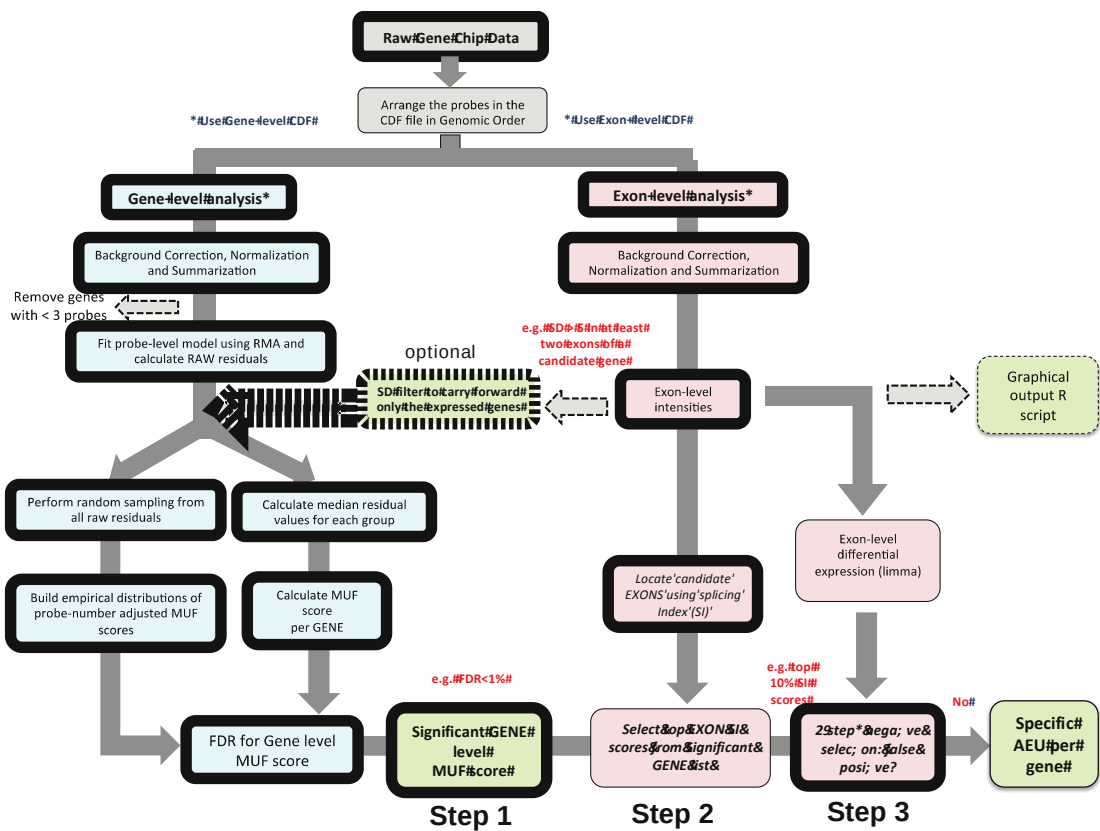


Figure 25. iGEMS analysis pipeline

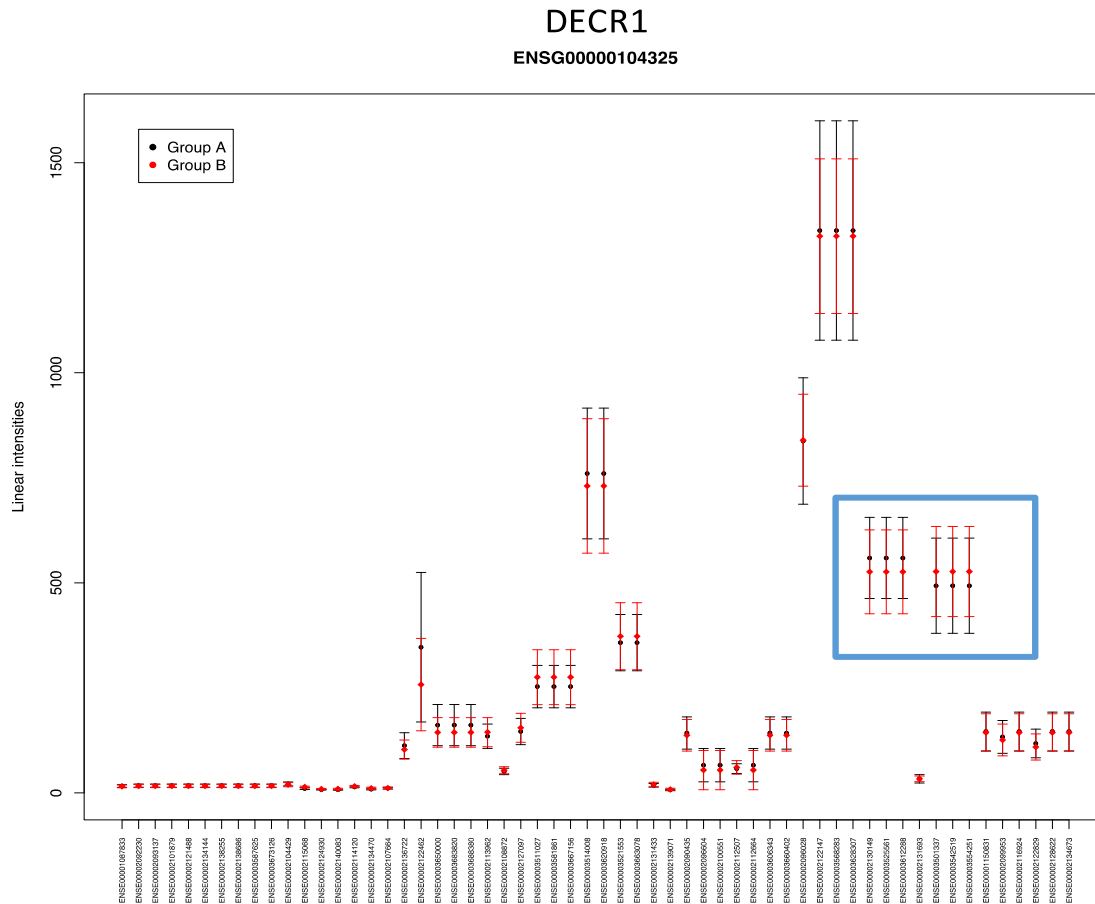


Figure 26. Plot of DECR1 in people with high versus low insulin sensitivity. The blue box indicates alternative splicing for several Exons.

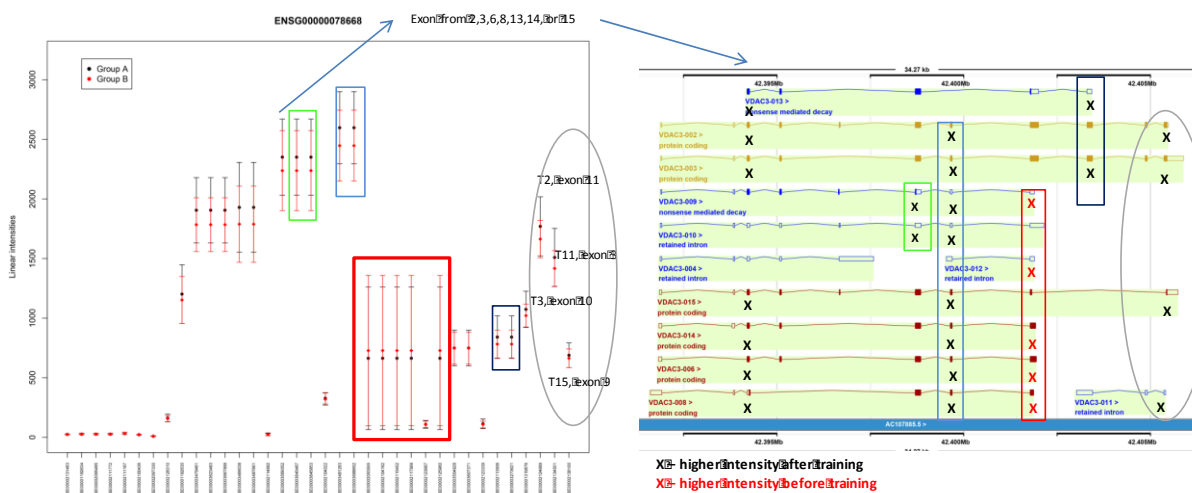


Figure 27. Application of iGEMS to muscle tissue related to high responders in VO2max

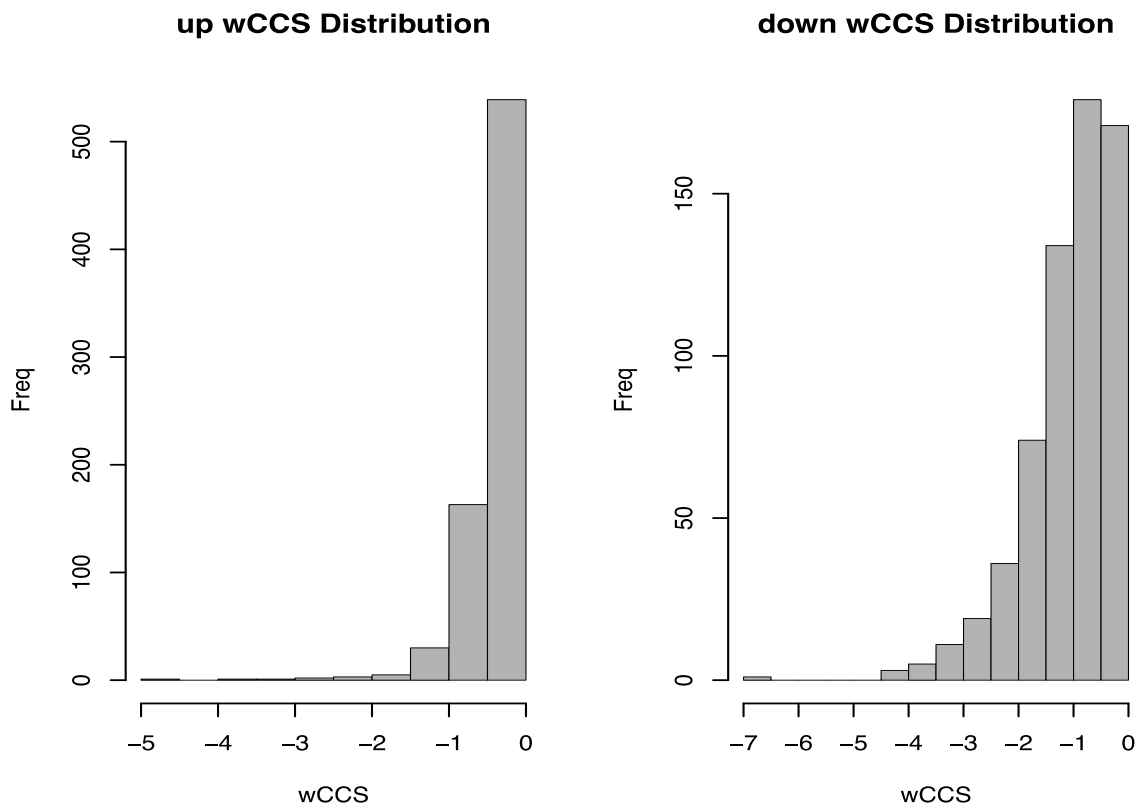


Figure 28. The wCCS for up and down regulated miRNAs WP5 D5.3 experiment.

