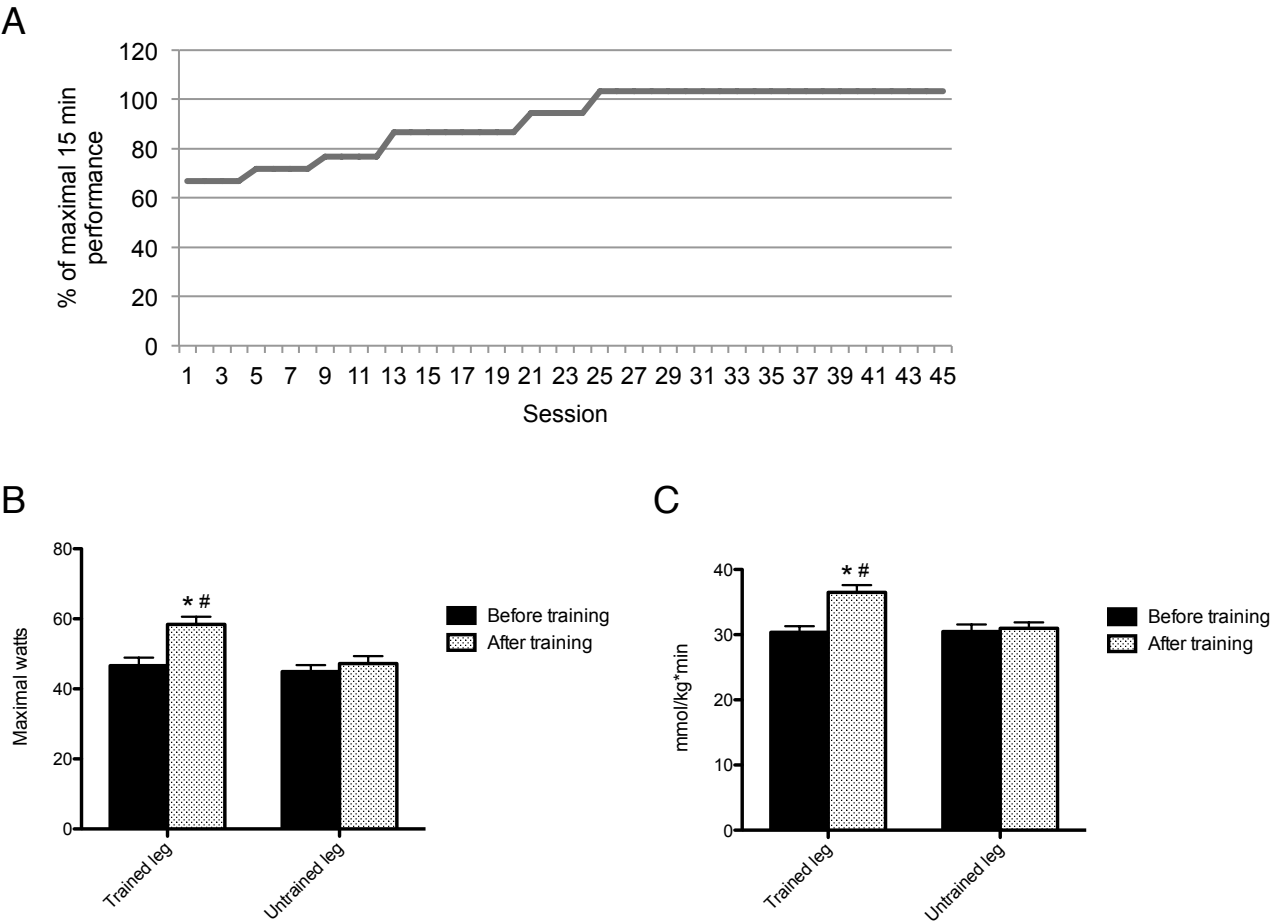


Figure S1. Training program and physiological characterization of training effect.
A) Load increase over the training period. B) Maximal one-leg performance test. C) β -HAD activity test. ANOVA post-hoc test, * $p < 0.001$ before vs. after training, # $p < 0.01$ trained vs. untrained leg



OXIDATIVE PHOSPHORYLATION

Complex I: NADH dehydrogenase (Thermus thermophilus). Components: FMN, Nqo4, Nqo5, Nqo9, Nqo1, Nqo2, Nqo3, Nqo6, Nqo7, Nqo8, Nqo10, Nqo11, Nqo12, Nqo13, Nqo14, Nqo15, Nqo16, Nqo17, Nqo18, Nqo19, Nqo20, Nqo21, Nqo22, Nqo23, Nqo24, Nqo25, Nqo26, Nqo27, Nqo28, Nqo29, Nqo30, Nqo31, Nqo32, Nqo33, Nqo34, Nqo35, Nqo36, Nqo37, Nqo38, Nqo39, Nqo40, Nqo41, Nqo42, Nqo43, Nqo44, Nqo45, Nqo46, Nqo47, Nqo48, Nqo49, Nqo50, Nqo51, Nqo52, Nqo53, Nqo54, Nqo55, Nqo56, Nqo57, Nqo58, Nqo59, Nqo60, Nqo61, Nqo62, Nqo63, Nqo64, Nqo65, Nqo66, Nqo67, Nqo68, Nqo69, Nqo70, Nqo71, Nqo72, Nqo73, Nqo74, Nqo75, Nqo76, Nqo77, Nqo78, Nqo79, Nqo80, Nqo81, Nqo82, Nqo83, Nqo84, Nqo85, Nqo86, Nqo87, Nqo88, Nqo89, Nqo90, Nqo91, Nqo92, Nqo93, Nqo94, Nqo95, Nqo96, Nqo97, Nqo98, Nqo99, Nqo100, Nqo101, Nqo102, Nqo103, Nqo104, Nqo105, Nqo106, Nqo107, Nqo108, Nqo109, Nqo110, Nqo111, Nqo112, Nqo113, Nqo114, Nqo115, Nqo116, Nqo117, Nqo118, Nqo119, Nqo120, Nqo121, Nqo122, Nqo123, Nqo124, Nqo125, Nqo126, Nqo127, Nqo128, Nqo129, Nqo130, Nqo131, Nqo132, Nqo133, Nqo134, Nqo135, Nqo136, Nqo137, Nqo138, Nqo139, Nqo140, Nqo141, Nqo142, Nqo143, Nqo144, Nqo145, Nqo146, Nqo147, Nqo148, Nqo149, Nqo150, Nqo151, Nqo152, Nqo153, Nqo154, Nqo155, Nqo156, Nqo157, Nqo158, Nqo159, Nqo160, Nqo161, Nqo162, Nqo163, Nqo164, Nqo165, Nqo166, Nqo167, Nqo168, Nqo169, Nqo170, Nqo171, Nqo172, Nqo173, Nqo174, Nqo175, Nqo176, Nqo177, Nqo178, Nqo179, Nqo180, Nqo181, Nqo182, Nqo183, Nqo184, Nqo185, Nqo186, Nqo187, Nqo188, Nqo189, Nqo190, Nqo191, Nqo192, Nqo193, Nqo194, Nqo195, Nqo196, Nqo197, Nqo198, Nqo199, Nqo200, Nqo201, Nqo202, Nqo203, Nqo204, Nqo205, Nqo206, Nqo207, Nqo208, Nqo209, Nqo210, Nqo211, Nqo212, Nqo213, Nqo214, Nqo215, Nqo216, Nqo217, Nqo218, Nqo219, Nqo220, Nqo221, Nqo222, Nqo223, Nqo224, Nqo225, Nqo226, Nqo227, Nqo228, Nqo229, Nqo230, Nqo231, Nqo232, Nqo233, Nqo234, Nqo235, Nqo236, Nqo237, Nqo238, Nqo239, Nqo240, Nqo241, Nqo242, Nqo243, Nqo244, Nqo245, Nqo246, Nqo247, Nqo248, Nqo249, Nqo250, Nqo251, Nqo252, Nqo253, Nqo254, Nqo255, Nqo256, Nqo257, Nqo258, Nqo259, Nqo260, Nqo261, Nqo262, Nqo263, Nqo264, Nqo265, Nqo266, Nqo267, Nqo268, Nqo269, Nqo270, Nqo271, Nqo272, Nqo273, Nqo274, Nqo275, Nqo276, Nqo277, Nqo278, Nqo279, Nqo280, Nqo281, Nqo282, Nqo283, Nqo284, Nqo285, Nqo286, Nqo287, Nqo288, Nqo289, Nqo290, Nqo291, Nqo292, Nqo293, Nqo294, Nqo295, Nqo296, Nqo297, Nqo298, Nqo299, Nqo300, Nqo301, Nqo302, Nqo303, Nqo304, Nqo305, Nqo306, Nqo307, Nqo308, Nqo309, Nqo310, Nqo311, Nqo312, Nqo313, Nqo314, Nqo315, Nqo316, Nqo317, Nqo318, Nqo319, Nqo320, Nqo321, Nqo322, Nqo323, Nqo324, Nqo325, Nqo326, Nqo327, Nqo328, Nqo329, Nqo330, Nqo331, Nqo332, Nqo333, Nqo334, Nqo335, Nqo336, Nqo337, Nqo338, Nqo339, Nqo340, Nqo341, Nqo342, Nqo343, Nqo344, Nqo345, Nqo346, Nqo347, Nqo348, Nqo349, Nqo350, Nqo351, Nqo352, Nqo353, Nqo354, Nqo355, Nqo356, Nqo357, Nqo358, Nqo359, Nqo360, Nqo361, Nqo362, Nqo363, Nqo364, Nqo365, Nqo366, Nqo367, Nqo368, Nqo369, Nqo370, Nqo371, Nqo372, Nqo373, Nqo374, Nqo375, Nqo376, Nqo377, Nqo378, Nqo379, Nqo380, Nqo381, Nqo382, Nqo383, Nqo384, Nqo385, Nqo386, Nqo387, Nqo388, Nqo389, Nqo390, Nqo391, Nqo392, Nqo393, Nqo394, Nqo395, Nqo396, Nqo397, Nqo398, Nqo399, Nqo400, Nqo401, Nqo402, Nqo403, Nqo404, Nqo405, Nqo406, Nqo407, Nqo408, Nqo409, Nqo410, Nqo411, Nqo412, Nqo413, Nqo414, Nqo415, Nqo416, Nqo417, Nqo418, Nqo419, Nqo420, Nqo421, Nqo422, Nqo423, Nqo424, Nqo425, Nqo426, Nqo427, Nqo428, Nqo429, Nqo430, Nqo431, Nqo432, Nqo433, Nqo434, Nqo435, Nqo436, Nqo437, Nqo438, Nqo439, Nqo440, Nqo441, Nqo442, Nqo443, Nqo444, Nqo445, Nqo446, Nqo447, Nqo448, Nqo449, Nqo450, Nqo451, Nqo452, Nqo453, Nqo454, Nqo455, Nqo456, Nqo457, Nqo458, Nqo459, Nqo460, Nqo461, Nqo462, Nqo463, Nqo464, Nqo465, Nqo466, Nqo467, Nqo468, Nqo469, Nqo470, Nqo471, Nqo472, Nqo473, Nqo474, Nqo475, Nqo476, Nqo477, Nqo478, Nqo479, Nqo480, Nqo481, Nqo482, Nqo483, Nqo484, Nqo485, Nqo486, Nqo487, Nqo488, Nqo489, Nqo490, Nqo491, Nqo492, Nqo493, Nqo494, Nqo495, Nqo496, Nqo497, Nqo498, Nqo499, Nqo500, Nqo501, Nqo502, Nqo503, Nqo504, Nqo505, Nqo506, Nqo507, Nqo508, Nqo509, Nqo510, Nqo511, Nqo512, Nqo513, Nqo514, Nqo515, Nqo516, Nqo517, Nqo518, Nqo519, Nqo520, Nqo521, Nqo522, Nqo523, Nqo524, Nqo525, Nqo526, Nqo527, Nqo528, Nqo529, Nqo530, Nqo531, Nqo532, Nqo533, Nqo534, Nqo535, Nqo536, Nqo537, Nqo538, Nqo539, Nqo540, Nqo541, Nqo542, Nqo543, Nqo544, Nqo545, Nqo546, Nqo547, Nqo548, Nqo549, Nqo550, Nqo551, Nqo552, Nqo553, Nqo554, Nqo555, Nqo556, Nqo557, Nqo558, Nqo559, Nqo560, Nqo561, Nqo562, Nqo563, Nqo564, Nqo565, Nqo566, Nqo567, Nqo568, Nqo569, Nqo570, Nqo571, Nqo572, Nqo573, Nqo

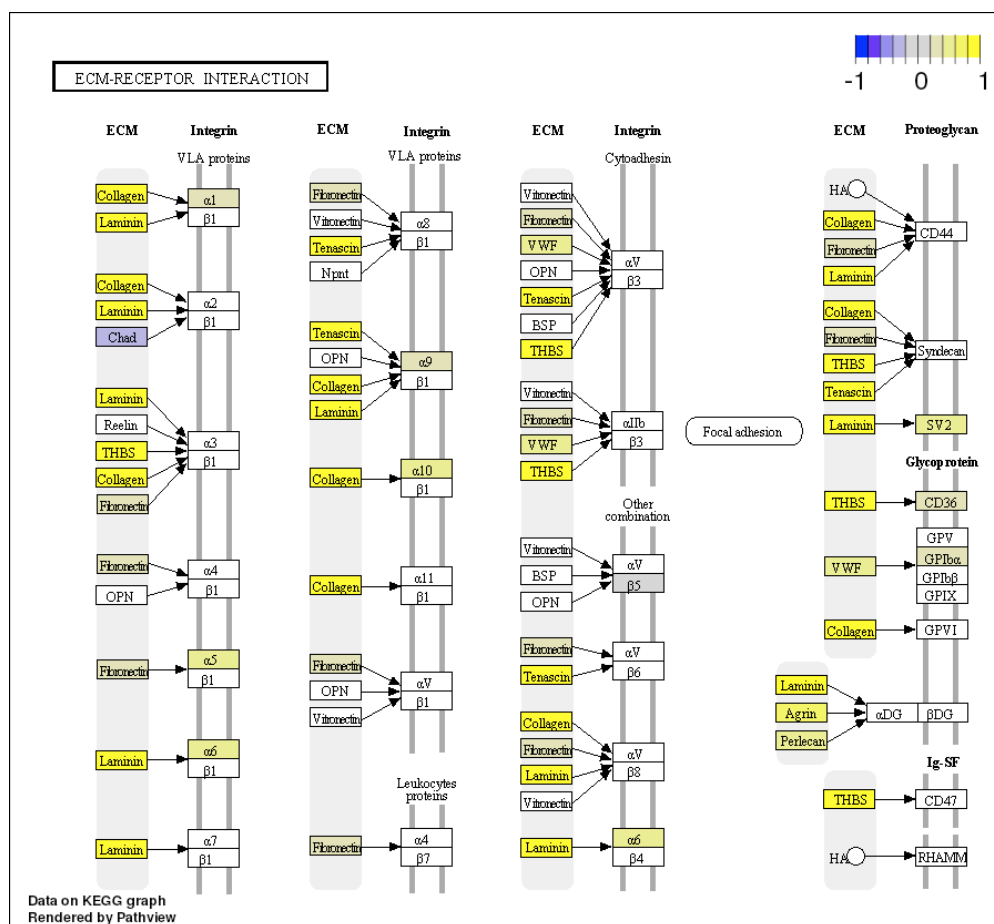


Figure S4. CpG sites correlating to the increase in citrate synthase activity. The standardized increase in Citrate Synthase (A) is significantly correlated to 631 sites changing in methylation (black dots in B). The clustering of the samples is shown by principal component analysis (C) using only significantly changing sites. A segment connects measurements from the same subject obtained before or after training. Samples are alternatively colored by group (T1=blue, T2=red) or by gender (M=green, F=magenta).

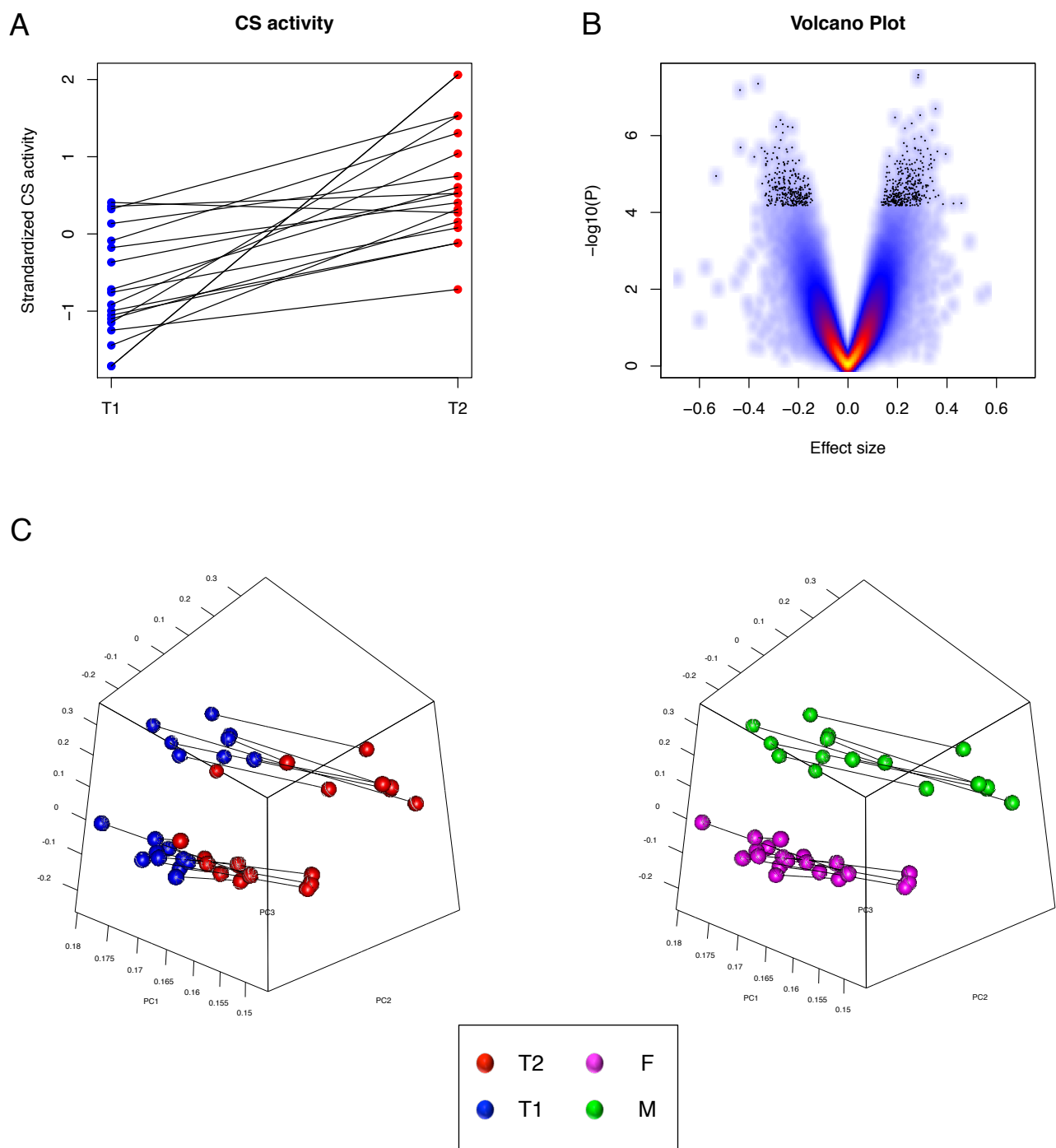


Figure S5. Global methylation and hydroxymethylation levels and technical validation of the 450K array data. A) Total % CCGG methylation analyzed with LUMA and B) total % hydroxymethylation measured colorimetrically. C) Regression analysis of the seven CpG sites from the array that were validated using bisulfite pyrosequencing. Three sites decreased in methylation with training according to the array D) HK3, E) IGFBP4 and F) THBS2. One non-changing IGFBP4 site was selected (F) and three sites increasing in methylation G) MYH3 (the second bar cluster is the same as the first but with one subject removed), H) CRYAB and I) MYOM2. The additional sites analyzed with the same primers are represented as +/- the number of base pairs from the site measured in the array. * Indicates significant difference compared to before training ($p < 0.05$), otherwise suggestive p-value is shown if $p \leq 0.1$.

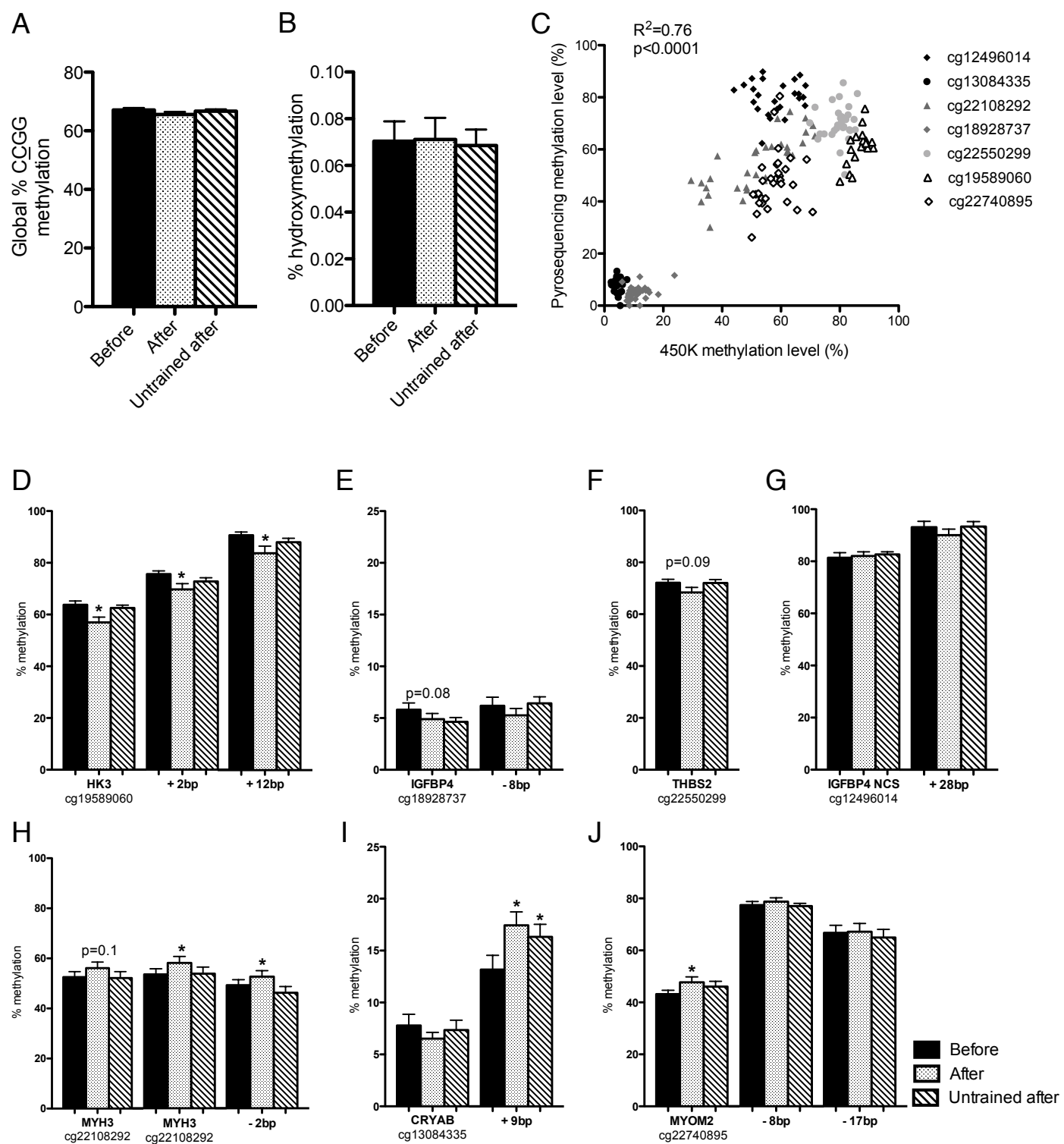
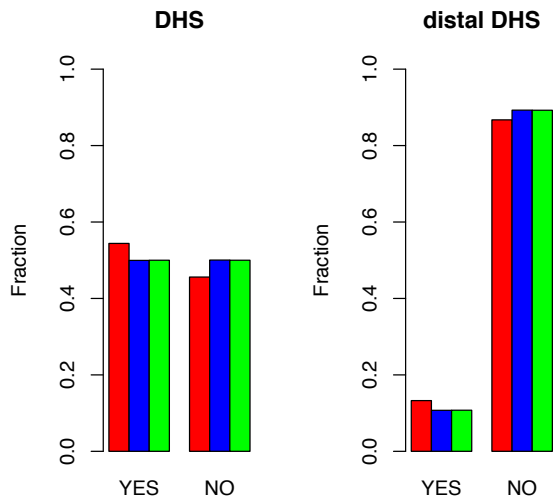


Figure S6. DNA methylation changes are primarily localized in regulatory regions.
For each annotation category, the relative fraction of positions located within each feature type is calculated for DMPs (red bars), non-DMPs (blue bars) and the entire position on the array (green bar).

DNase Hypersensitivity Sites

Using ENCODE DHS in 125 cell and tissue types
(Thurman et al. Nature 2012)



Promoters

Using NIH Roadmap Epigenomics
ChIP-Seq from Skeletal Muscle

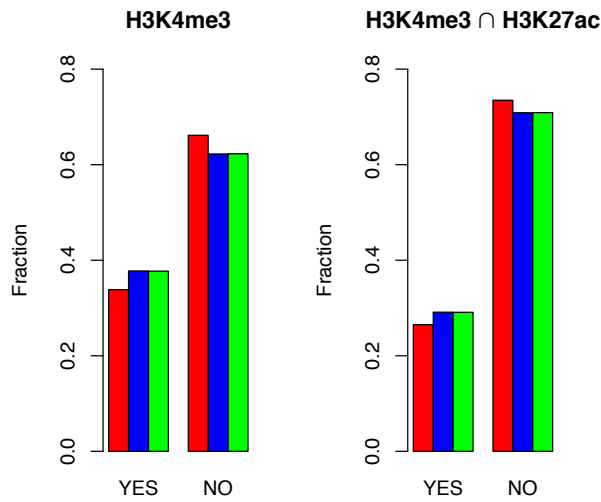


Figure S7. Network analysis of gene expression. A transcriptional network was reconstructed using RNA expression data, showing three major domains (see Methods). The color indicates the log2FC.

Domain A
Regulation of gene expression

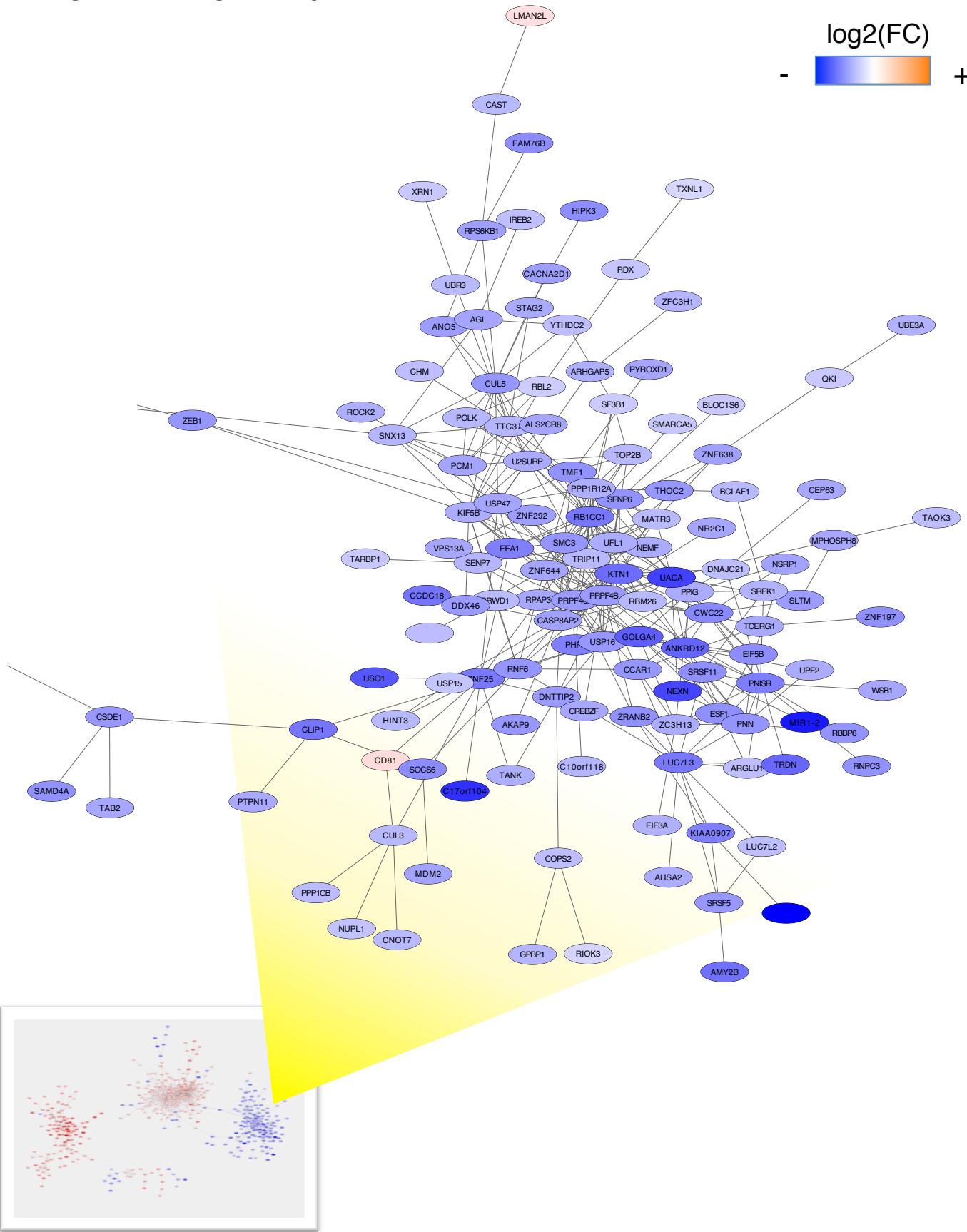


Figure S7. (continued)

Domain B
Cellular energetics

log2(FC)

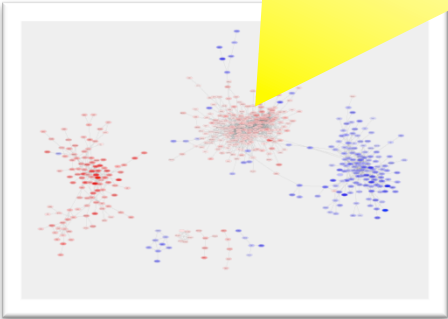
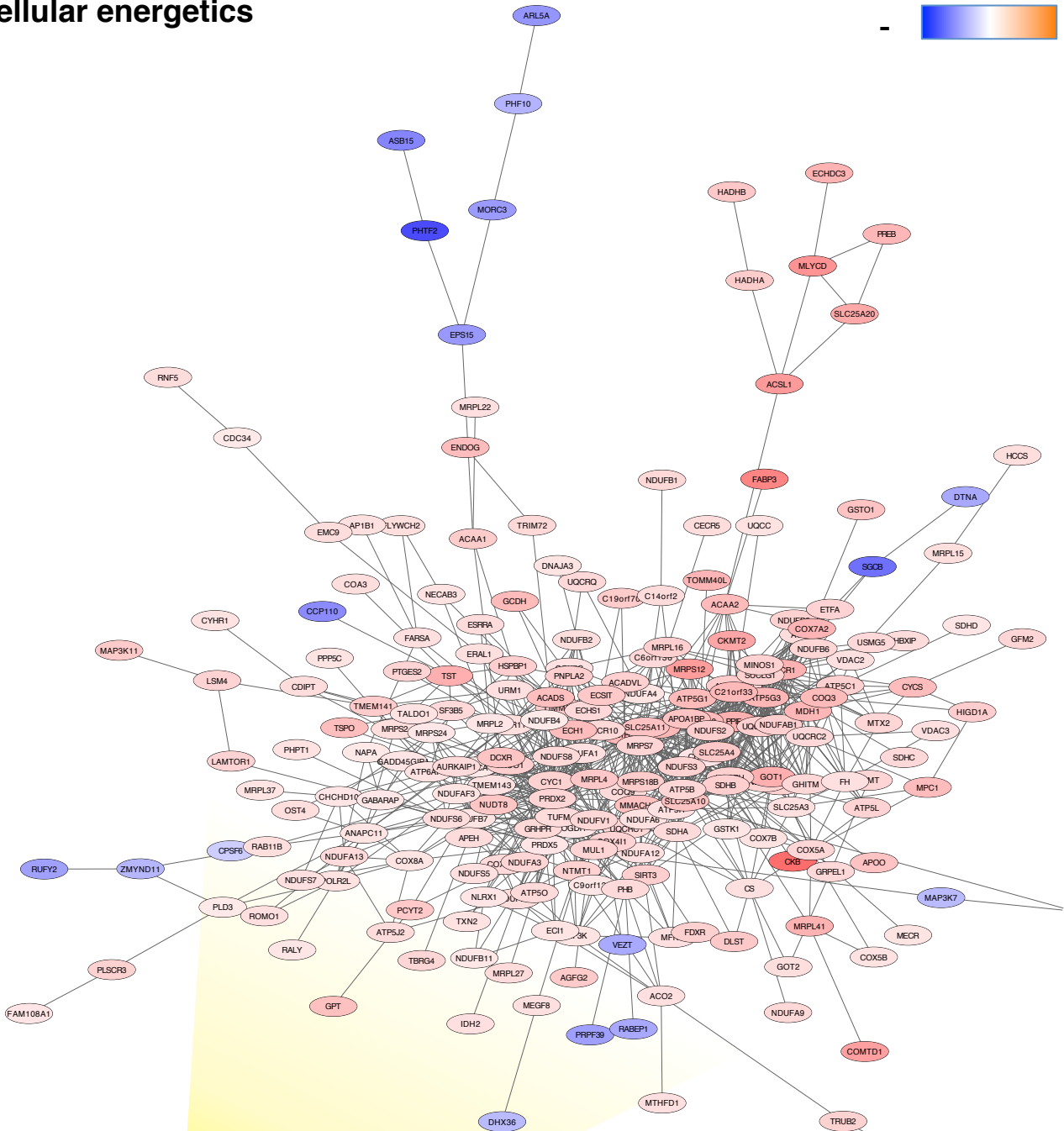


Figure S7. (continued)

Domain C
Morphological changes

log2(FC)

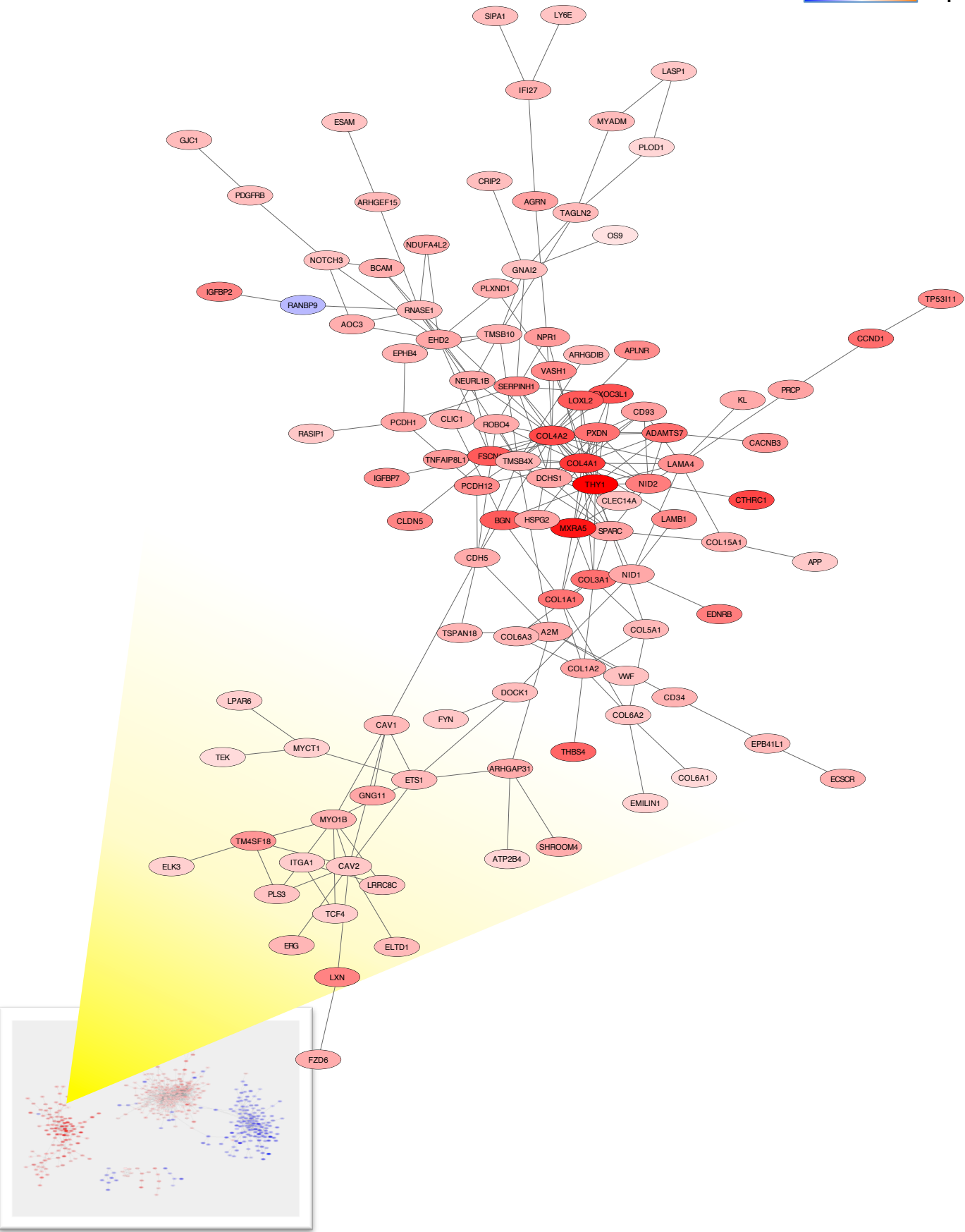


Figure S7. (continued)

Minor domains

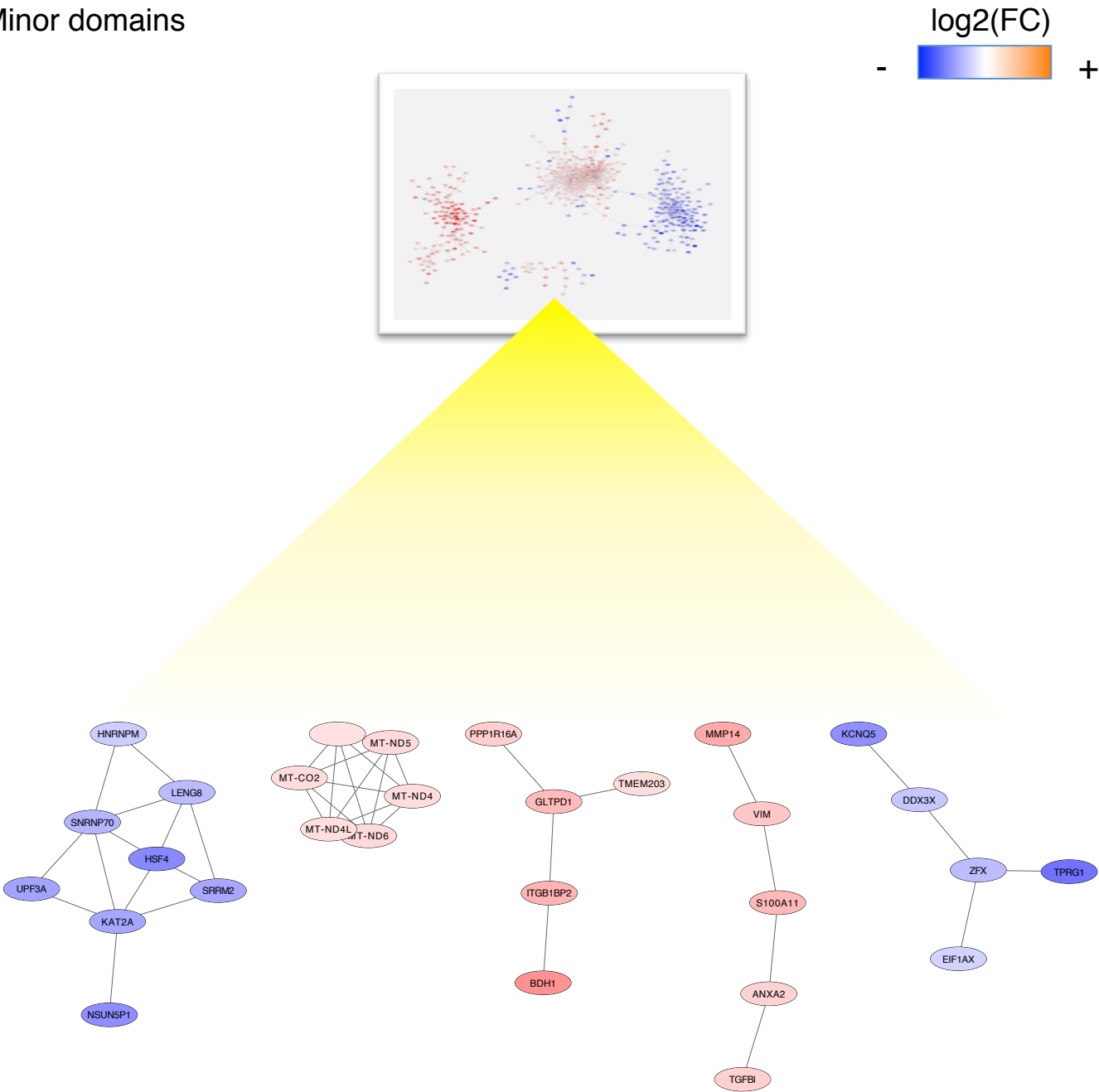


Figure S8. QQ-plot for DNA methylation analysis. A QQ-plot as a guide for interpreting the results and it is given below. Theoretical quantiles from a t-distribution are compared against the observed t-statistics from limma analysis. Some signs of inflation are revealed and possible interpretations include: a) dependency between tested CpG, as it is accepted that they could be spatially and temporally correlated; b) presence of outliers or bad quality samples, but difficult to identify, despite quality control was thoroughly performed and all the samples included in the final dataset show satisfying quality; c) residual batch effect. The samples have been corrected by known sources of batch effect, however we cannot establish if the effect was mitigated but not completely removed

