Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study

Davina J Hensman Moss* , Antonio F. Pardiñas*, Douglas Langbehn, Kitty Lo, Blair R. Leavitt, Raymund Roos, Alexandra Durr, Simon Mead, Peter Holmans, Lesley Jones[§], Sarah J Tabrizi[§] and the REGISTRY and the TRACK-HD investigators. *Contributed equally; [§]Contributed equally.

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Methods

Defining progression in TRACK-HD

Among the wide variety of potential cognitive and quantitative-motor variables, we analysed a subset of those that were previously used in a 36-month predefined primary analysis(1). A small number of quantitative-motor variables that were substantively redundant were eliminated and those with more tractable metric properties were chosen (**Supplementary Table 2**).

For the Track HD study, 10 subjects were excluded because they had no follow-up data. 15 other subjects were excluded because of missing brain MRI data there was no missing data for the other variables used in the analysis.

Our models controlled for study site, gender, education, and their interactions with follow-up time, consistent with the models used in the TRACK-HD standard analyses which are described elsewhere(1-4). The dominance of the first principal component is shown in the Scree plot in **Supplementary Figure 9**.

Progression analysis in REGISTRY

We used a square-root transform of TMS to improve approximate multivariate normality of the data. Missing data were considerable as documented **Supplementary Table 15**.

To deal with the missing data for clinical items, multiple imputation with 25 imputations was performed. Age, gender, and CAG expansion length were auxiliary variables for the imputations. Proper methods to account for imputation variation were used for all statistical inferences. Final parameter estimates and statistical significance were estimated by Rubin's method(5). We performed the above using the MI and MIANALYZE procedures of SAS/STAT 13.1(6).

In order to generate atypical severity scores, we needed to undertake three sequential procedures: (i) Multiple imputation of missing data (ii) Principal Component Analysis (PCA) and severity scoring of the combined imputed data replications (iii) Regression of the predictive effect of age, CAG length, and gender on the PCA-derived severity scores so that we are left with a measure of atypical (or “unexplained”) severity. The steps were taken in the order above; given that these steps could be done in different orders we also confirmed that there were only minimal differences due to the order (*data not shown*). We also noted some evidence of study site effects in the eventual regressions. Thus we used a random effect for site in models adjusting for age and CAG. Atypical severity was defined as the residual between each subject's observed and marginal predicted value. The dominance of the first principal component is shown in **Supplementary Figure 10**.

The final averaged multiple imputation model used a 2 degree of freedom restricted cubic spline(7) of cumulative probability of onset (CPO), plus main effects of gender and CAG length and a random effect for

site. Marginal effects from this model, which represent the estimated effects after accounting for site fluctuations, were used for all predictions. The knot placement for the clinical probability of onset spline was defined a priori using a conventional standard at the 10^{th}, 50^{th}, and 90^{th} percentiles of its observed distribution. The corresponding values were (0.131, 0.395, 0.885). Atypical severity was defined as the residual between each subject's observed and marginal predicted value. Final parameter estimates, along with estimates of statistical significance adjusted for the multiple imputation procedure are shown in the **Supplementary Table 16**.

We inspected the potential biasing influence of the CAG repeats, by classifying the individual in short (CAG < 41) and long (CAG > 55) repeats. We found an overrepresentation of people with larger atypical severity scores among those with short CAG, which implies that those with a small number of repeats are more likely to be in the study if atypically severely affected. This is likely to be due to the disease only being partially penetrant in those with short CAG repeats, resulting in bias (8). This prompted us to exclude subjects with short CAG from the creation of the severity scores, while retaining those with long CAG. However, we confirmed that the age-CAG severity function predicted using CAG > 41 gave sensible estimates for both the short and long ranges, enabling even those subjects with short CAG to be used in the final analysis (**Supplementary Figure 11)**.

Comparing TRACK-HD and REGISTRY progression measures

There are four common measures between TRACK-HD and REGISTRY: TMS, symbol digit score, Stroop word reading score and TFC. We took the first principal component score from an analysis of these four measures at the last TRACK-HD visit: this accounted for 79.4% of the variance in the PCA and correlated approximately equally with each of the four observed variables (**Supplementary Table 21**). To calculate the measure of severity unaccounted for by age and CAG length in TRACK, we regressed these principal component scores on the same predictors used for the unified REGISTRY progression measure, to give TRACK-HD severity scores.

As explained in the manuscript page 13, within the TRACK-HD data, the last-visit severity scores had a Pearson correlation of 0·674 with the previously calculated longitudinal progression measure. It can be shown that the predicted values obtained from the TRACK-HD and REGISTRY formulas are nearly linear, hence that Pearson correlation should be an adequate descriptive statistic for the relationship (**Supplementary Figure 12**).

Genotyping and quality control

DNA was obtained from blood samples of the 218 TRACK-HD study participants who had complete serial phenotype data, using standard methods (2). Genotyping was performed in Illumina Omni2.5 v1.1 arrays at

UCL Genomics, in accordance with the Infinium LCG Assay (15023141_A, June 2010) protocol (Illumina Inc, San Diego, USA). Standard QC procedures (9) were performed using PLINK v1.9 (10), including controlling for coverage and call rates (5% of missing data allowed per SNP and individual), inbreeding ($F < 0.2$ required) and Hardy-Weinberg equilibrium (SNPs with $p < 10^{-6}$ in an exact test were removed). With these criteria, and after removing one individual of a twin pair, a total of 216 gene positive TRACK-HD subjects were left in the sample, genotyped for 2.34 million genome-wide markers (**Figure 1**).

Identity-by-descent analysis showed 9 pairs of individuals with a relatedness coefficient ($\hat{\pi}$) higher than 0.15, which included 6 putative first degree relatives, 2 putative second degree relatives and 1 putative pair of third degree relatives. Additionally, an ADMIXTURE analysis with a subset of the 1000 Genomes (11) populations revealed 6 individuals with more than 25% of non-European ancestry. All these individuals were retained in the TRACK-HD sample, as their relatedness and admixture can be accommodated well by using association methods based on mixed linear models (12, 13).

TRACK-HD was imputed in the Cardiff University high-performance computing cluster RAVEN(14), using the SHAPEIT/IMPUTE2 algorithms(15, 16) and a standardised pipeline(17). The 1000 Genomes phase 3 panel provided by the IMPUTE2 authors (release October 2014), was used as the reference imputation panel. Imputation probabilities ("dosages") were converted to best-guess genotypes in fcGENE v1.07(18) using a minimum probability threshold of 80% and a per-SNP missingness threshold of 5% of the sample. After this process an INFO score cutoff of 0.8 was applied in order to select well-imputed variants, and all monomorphic and singleton markers were excluded. With these filters 9.65 million biallelic markers remained in the dataset.

Genotypes for the REGISTRY subjects were obtained from the GeM-HD Consortium (19), where details of their genotyping, curation and imputation are provided. This dataset harboured 8.94 million biallelic markers of 1,773 individuals (**Figure 1**).

Mixed linear model GWAS

Association analyses were performed with the mixed linear model (MLM) functions included in GCTA v1.26(20), specifically the leave-one-chromosome-out (LOCO) procedure(21). As the genetic relationship matrix used by MLMs can accurately account for cryptic relatedness and ancestry, and phenotypic variables already controlled for relevant clinical covariates, no covariates were added to the analyses. In order to transform the results into independent GWAS signals, PLINK was again used to perform linkage disequilibrium (LD) clumping ($r^2 = 0.1$, $p < 1x10^{-4}$; window size < 3 Mb). Due to the relatively small size of the TRACK-HD and REGISTRY samples, calculation of SNP-based heritability (h^2_{SNP}) for our tested phenotypes was not possible using either genotyped or imputed markers(22, 23). Because of the small sample sizes, analyses were restricted to SNPs with minor allele frequency >1%.

Meta-analysis of the GWAS summary statistics from the TRACK-HD and REGISTRY studies was carried out using the fixed effects method with inverse-variance weights as implemented in METAL (24). The meta-analysis of TRACK-HD and REGISTRY studies was carried out using the fixed effects method with inverse-variance weights as implemented in METAL(24). To control for spurious results due to scale differences between the TRACK-HD and REGISTRY progression phenotypes, effect sizes from both summary statistics were standardised to have equal variances before meta-analysis.

QQ plots of observed log p-values (sorted by value) for each SNP versus their expected values in the absence of association are shown for TRACK-HD, REGISTRY and the meta-analysis in **Supplementary Figure 13**. If there is no association, and no systematic inflation in the test statistics (for example, from population stratification), the observed log p-values would follow their expected values (the red line in **Supplementary Figure 13**) exactly. Indeed, this is what is observed for the majority of data points, which do not show association. The extent to which such systematic inflation exists is measured by the genomic inflation factor λ (25), which is the median of the observed test statistics divided by 0.456 (the median of a chi-squared distribution on 1df). Values of λ close to 1 – as is the case here – indicate a lack of inflation. The 95% confidence interval for log p-values in the absence of association is shaded grey, and the points lying above this in the top right corner indicate genuine associations.

Conditional analyses of GWAS summary statistics were carried out using the COJO procedure included in GCTA v1.26(26).

Co-localisation analyses

In order to discern if our top GWAS signals were mediated by the same SNPs in both TRACK-HD and REGISTRY, we used the co-localisation method of Giambartolomei *et al*.(27), as implemented in GWAS-pw v0.21 (28). In summary, the GWAS summary statistics of our two samples were first divided into approximately independent LD blocks(29), and each block was then scanned to estimate the probability (in a hierarchical Bayesian framework) of harbouring an association common to the two samples. In contrast to the original algorithm, the model priors do not need to be pre-specified in GWAS-pw, as they are estimated directly from the summary statistics. This implementation has been thoroughly tested by simulation and applied to real data from heterogeneous sources (28). By testing the entire genome instead of a small number of candidate regions arising from the GWAS clumps, we follow a conservative approach towards estimating co-localisation, which also has the desirable property of allowing us to compare our candidates (to the resolution of single SNPs) with every other region in the genome.

A similar procedure was used to test for co-localisation between the region on chromosome 5 containing GWAS signal in TRACK-HD and REGISTRY and SNPs influencing expression (eQTLs), since this may indicate which gene in an association region is causal. Given that eQTLs close to the gene (cis-eQTLs) tend to replicate more reliably than those from other parts of the genome (30), these analyses were restricted to

the regions of GWAS signal and genes within 1Mb of these regions. These analyses used expression data from 53 tissues, accessed through GTeX (31). To minimise multiple testing, the two tissues showing the most significant eQTLs for each gene were used for the co-localisation analysis. Additionally, for DHFR and MSH3, analyses were performed using three brain tissues (caudate, cerebellum and cortex), since these are the most biologically relevant to HD a priori. Co-localisation results are shown for the TRACK-HD GWAS in **Supplementary Table 8**, and the REGISTRY GWAS in **Supplementary Table 9**. Plots of GWAS and eQTL signals with significant co-localisation are shown in in **Supplementary Figures 7 and 8.**

Gene-based and gene-set analyses

Gene-wide p-values were calculated using MAGMA v1.05 (32) on the TRACK-HD and REGISTRY summary statistics, by summing the p-values of all SNPs inside each gene. MAGMA aggregates the association evidence across all SNPs in a gene, while correcting for LD between SNPs (using the European data from Phase 3 of the 1000 Genomes Project as reference). This analysis increases power when a gene contains multiple causal SNPs (e.g. as a result of allelic heterogeneity), or when the causal SNP is not typed and its signal is partially captured by multiple genotyped SNPs in LD with it. We set a window of 35 kb upstream and 10 kb downstream of each gene in order to capture the signal of proximal regulatory SNPs(33, 34).

To maximise comparability with the GeM GWAS, our primary gene-set analyses used Setscreen (Moskvina et al. 2011). Setscreen sums the (log-) p-values of all SNPs in the gene set, similar to Fisher's method, but adjusts the distribution to allow for non-independence of SNPs due to linkage disequilibrium (Brown 1975). Significant enrichments from the Setscreen analyses were confirmed using the competitive gene-set analysis procedure implemented in MAGMA. This more conservative approach tests whether genes in a gene set have more significant gene-wide p-values than other genes, correcting for gene size, SNP density and intergenic linkage disequilibrium (de Leeuw et al. 2015), but may be less powerful than the Setscreen analysis for small gene sets.

Initially, we performed gene set analyses on the 14 pathways found to be significantly enriched for association signal in the GeM GWAS. Many of these pathways relate to DNA repair, so we investigated the biological specificity of this signal further by analysing 78 gene-sets taken from a recent review of DNA repair (Pearl et al 2015).

As a secondary analysis, to potentially uncover areas of novel disease-related biology, we tested the same gene sets used by GeM-HD Consortium (2015). This comprises a collection of 14,706 pathways containing between 3 and 500 genes from the Gene Ontology (GO)(35), Kyoto Encyclopedia of Genes and Genomes (KEGG)(36), Mouse Genome Informatics (MGI)(37), National Cancer Institute (NCI)(38), Protein ANalysis THrough Evolutionary Relationships (PANTHER)(39), BioCarta(40) and Reactome(41). Multiple testing correction was carried out for this analysis by calculating q-values (Storey and Tibshirani, 2003).

Linking genetic variation to clinical measures

To explain how our TRACK-HD lead variant (rs557874766) affected commonly used clinical measures of HD severity we first correlated TRACK-HD progression score with UHDRS Total Motor Score (TMS) and UHDRS Total Functional Capacity (TFC). We defined "raw" TMS rate as TMS change divided by follow-up years and "adjusted" TMS rate as the residual of raw TMS rate after regressing off effects of initial TMS, age, sex, CAG. We followed the same procedure for TFC.

Regressing these measures on progression gives the following estimates of the amount of change for one unit increase in progression (standard errors in brackets):

Raw TMS rate: 0.71(0.19)
Adjusted TMS rate: 0.57 (0.18)
Raw TFC rate: 0.21 (0.047)
Adjusted TFC rate: 0.20 (0.044)

The effect size at the top MSH3 SNP in TRACK (rs557874766) is -0.58 (s.e. =0.087) units of progression per copy of the minor allele G (see **Supplementary Table 21**) – this corresponds to a change of -0.33 (95% CI =0.10, 0.56) to -0.41 (0.16,0.66) units in TMS rate compared to the major allele C, which can be interpreted as a reduction in the rate of TMS increase by 0.33-0.41 units per year for each copy of the G allele. Similarly, this corresponds to a reduction in the rate of TFC change of 0.12 (0.06,0.18) units per year per G allele.

Results

Since *MSH3* is a member of all the most significantly enriched pathways, we tested whether *MSH3* was individually responsible for the pathway enrichments by removing it and repeating the analyses. GO:32300 and KEGG:3430 are still nominally significant in TRACK (p=0.0413, p=0.0452 respectively) but not in REGISTRY. Neither of the two Pearl pathways is significant in TRACK or REGISTRY. The only pathways nominally significant both in TRACK and REGISTRY are GO:32389 (MutLalpha complex) and Pearl pathway "Repair_pathway/SSR/MMR/MutL_homologs", neither of which contain *MSH3*. Thus, it appears that the mismatch repair pathway enrichments are mainly driven by *MSH3*. However, in the TRACK-REGISTRY meta-analysis, the Pearl et al. MMR pathway ($p=1.27\times10^{-4}$), GO:32300 ($p=1.02\times10^{-3}$), KEGG 3430 (1.07×10^{-4}) and GO:30983 are at least nominally significant without *MSH3*. Pathway enrichments without *MSH3* are shown in **Supplementary Table 18** for the 14 GeM pathways and **Supplementary Table 19** for the Pearl et al. pathways.

Setscreen gene set analysis of the large set of pathways analysed by the GeM-HD Consortium (2015) is shown in **Supplementary Table 24.** There were 26 pathways showing significant ($q<0.05$) enrichment in

TRACK after correction for multiple testing of pathways. These pathways mainly relate to DNA repair and binding, and none is more significant than GO:32300 (mismatch repair complex). The genes in these 26 pathways are shown in **Supplementary Table 25,** and are similar to those in Tables 2 and 3, with the exception of DHFR (however, the pathways containing DHFR tend to be less strongly associated than the mismatch repair pathways in both TRACK and REGISTRY). Thus, analysis of the large set of pathways does not appear to throw up any novel areas of biology outside those indicated by the GeM paper.

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The TRACK-HD Investigators

CANADA
University of British Columbia, Vancouver: A Coleman, R Dar Santos, J Decolongon, A Sturrock

FRANCE
APHP, Hôpital Salpêtriere, Paris: E Bardinet, C Jauff ret, D Justo, S Lehericy, C Marelli, K Nigaud, R Valabrègue

NETHERLANDS
Leiden University Medical Centre, Leiden: SJA van den Bogaard, E M Dumas, J van der Grond, EP t'Hart, C Jurgens, M-N Witjes-Ane.

U.K.

St Mary's Hospital, Manchester: N Arran, J Callaghan, C Stopford;
London School of Hygiene and Tropical Medicine, London: C Frost, R Jones;
University College London, London: N Hobbs, N Lahiri, R Ordidge, G Owen, T Pepple, J Read, M Say, E Wild, A Patel, N C Fox, C Gibbard, I Malone, H Crawford, D Whitehead;
Imperial College London, London: S Keenan;
IXICO, London: D M Cash;
University of Oxford, Oxford: C Berna

GERMANY
University of Münster, Münster: N Bechtel, S Bohlen;
University of Bochum, Bochum: A Hoff man, P Kraus.

U.S.A.
University of Iowa, Iowa City, IA: E Axelson, C Wang, T Acharya (University of Iowa, Iowa City, IA);
Massachusetts General Hospital, Harvard, MA: S Lee, W Monaco
Indiana University, IN: C Campbell, S Queller, K Whitlock.

AUSTRALIA
Monash University, Victoria: C Campbell, M Campbell, E Frajman, C Milchman, A O'Regan, I Labuschagne

The REGISTRY Investigators 2004-2012

Registry Steering committee: Anne-Catherine Bachoud-Lévi, Anna Rita Bentivoglio, Ida Biunno, Raphael Bonelli, Jean-Marc Burgunder, Stephen Dunnett, Joaquim Ferreira, Olivia Handley, Arvid Heiberg, Torsten Illmann, G. Bernhard Landwehrmeyer, Jamie Levey, Maria A. Ramos-Arroyo, Jørgen Nielsen, Susana Pro Koivisto, Markku Päivärinta, Raymund A.C. Roos, A Rojo Sebastián, Sarah Tabrizi, Wim Vandenberghe, Christine Verellen-Dumoulin, Tereza Uhrova, Jan Wahlström+, Jacek Zaremba

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U.K.

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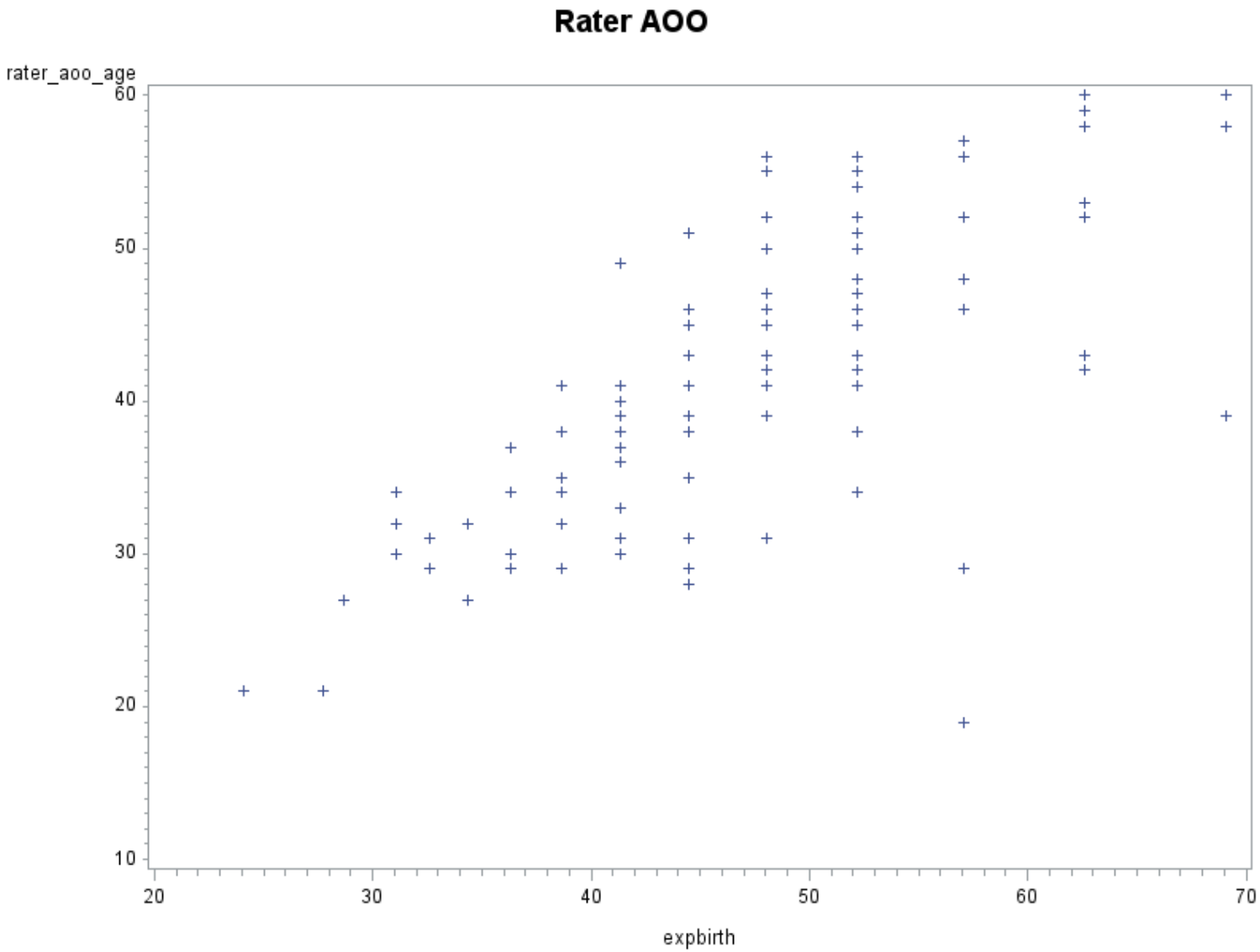
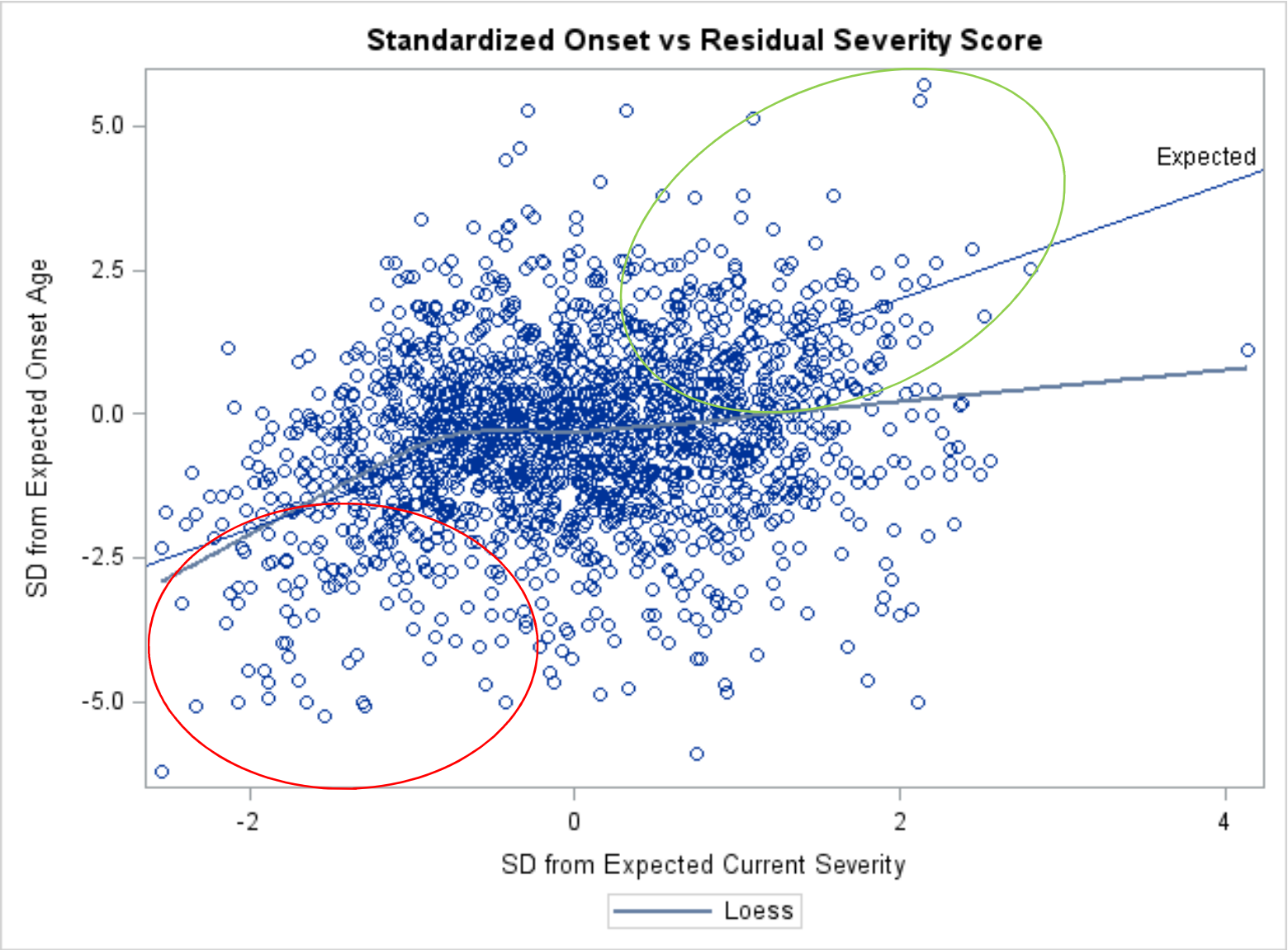
EHDN's associate site in SINGAPORE: National Neuroscience Institute Singapore: Jean-Marc Burgunder, Puay Ngoh Lau, Emmanul Pica, Louis Tan

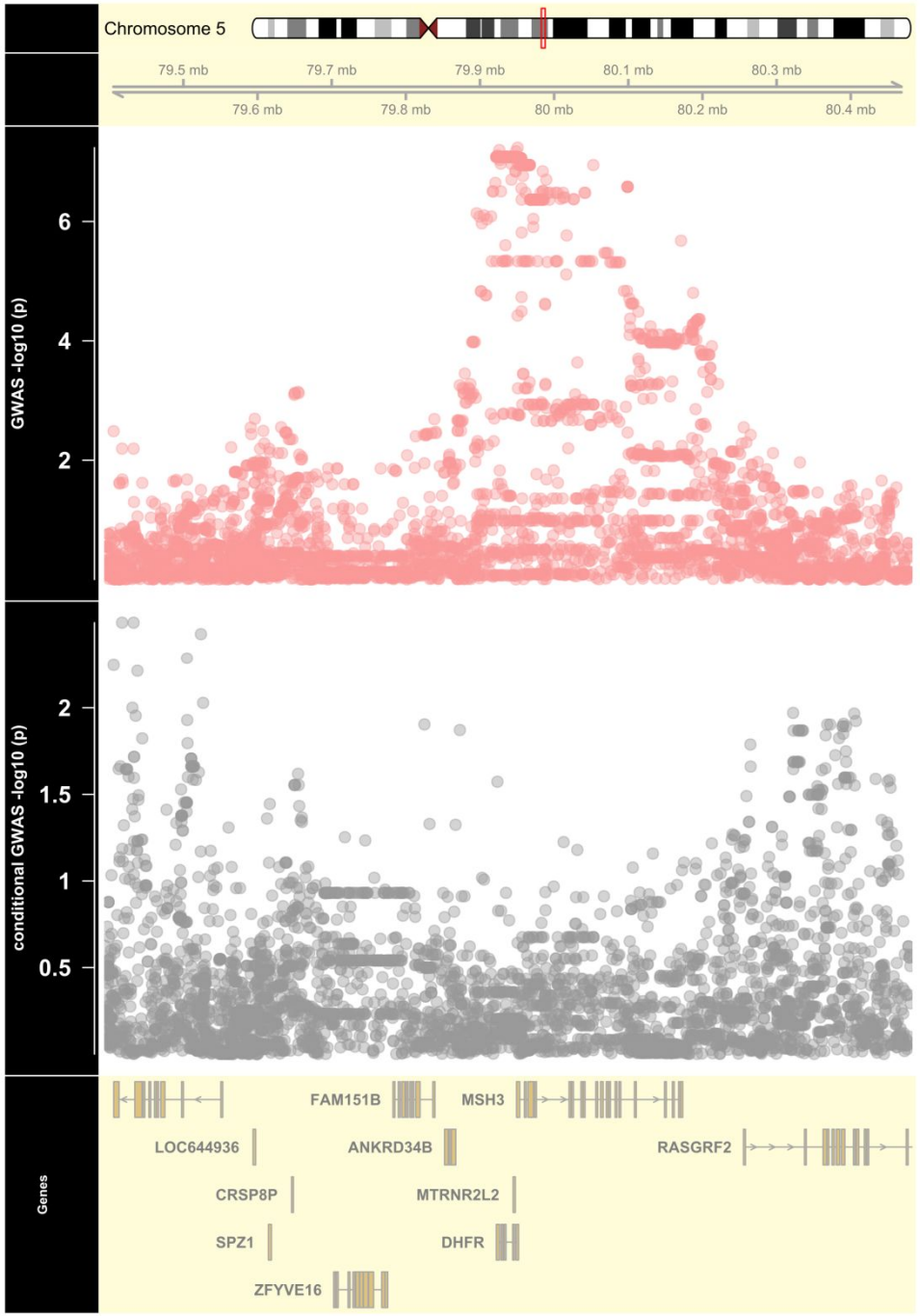
Supplementary Figure 1: Observed versus Expected Age of Onset Among Those Who Have Experienced Onset in the TRACK-HD analysis: amongst these 96 subjects who had experienced onset, the rater AAO showed the expected relation with predicted AAO based on CAG length. Earlier than predicted onset age was correlated with faster progression (using the unified HD progression measure) (r=-0·315; p = 0·002)

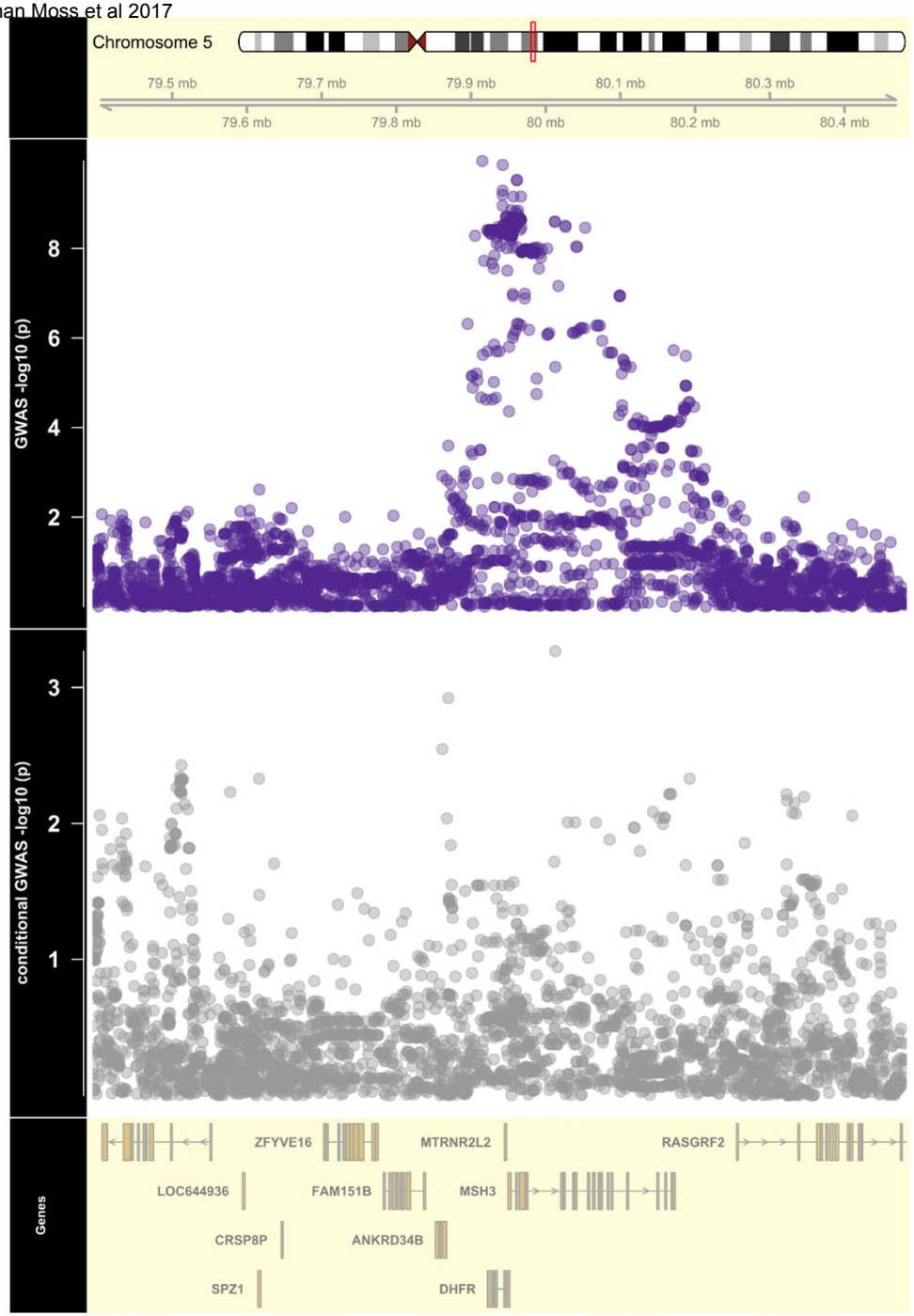


Supplementary Figure 2: REGISTRY progression measure and atypical onset age are modestly correlated in REGISTRY. Note bias for very late expected onset for those with low CAG repeats. SD = Standard deviation.



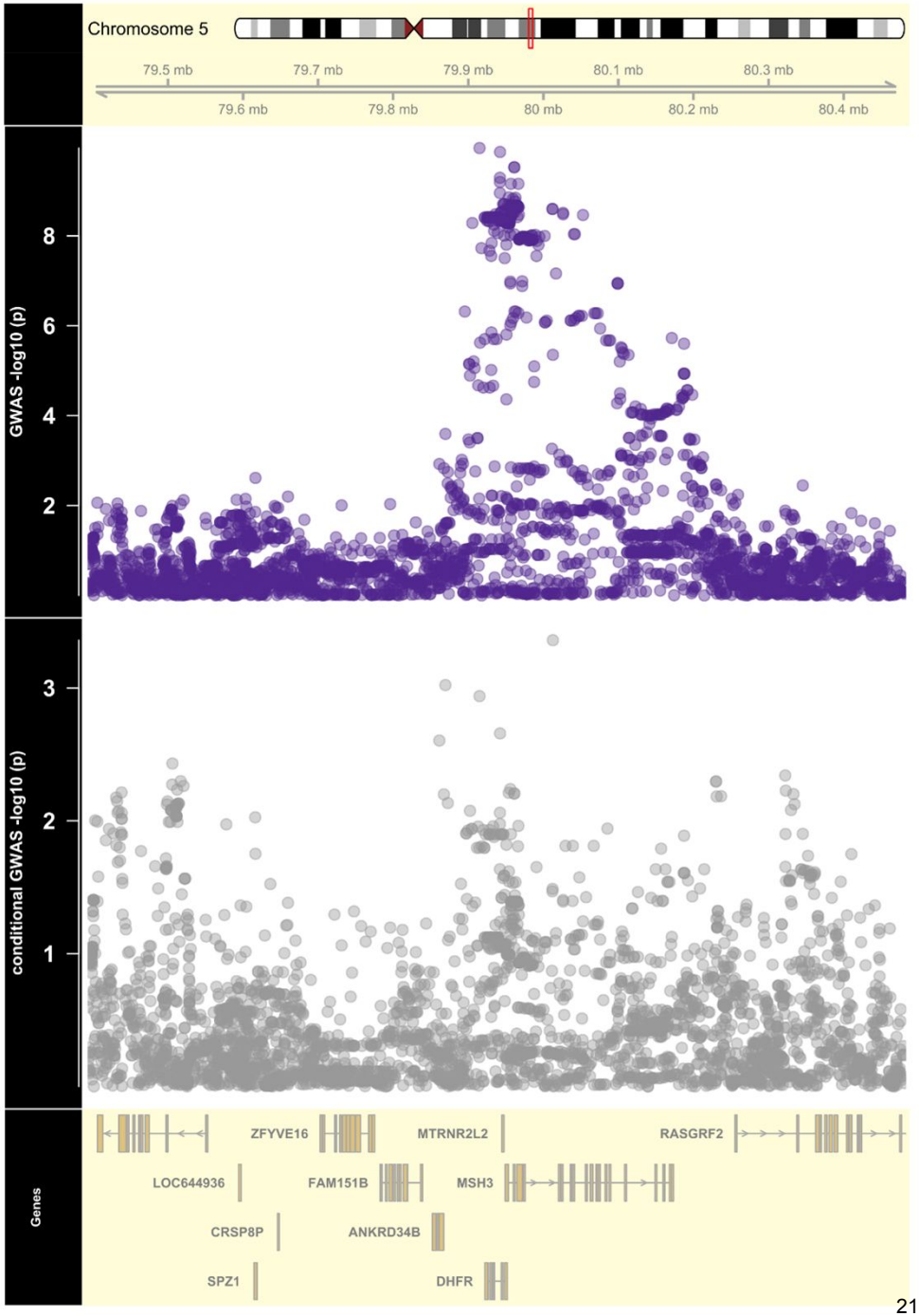
Supplementary Figure 3: Regional plot of TRACK-HD GWAS signal in the MSH3-DHFR region before(top) and after (bottom) conditioning on the most significant SNP in TRACK-HD (rs557874766). The lack of significant association after conditioning on this SNP is consistent with here being only one association signal in the region.



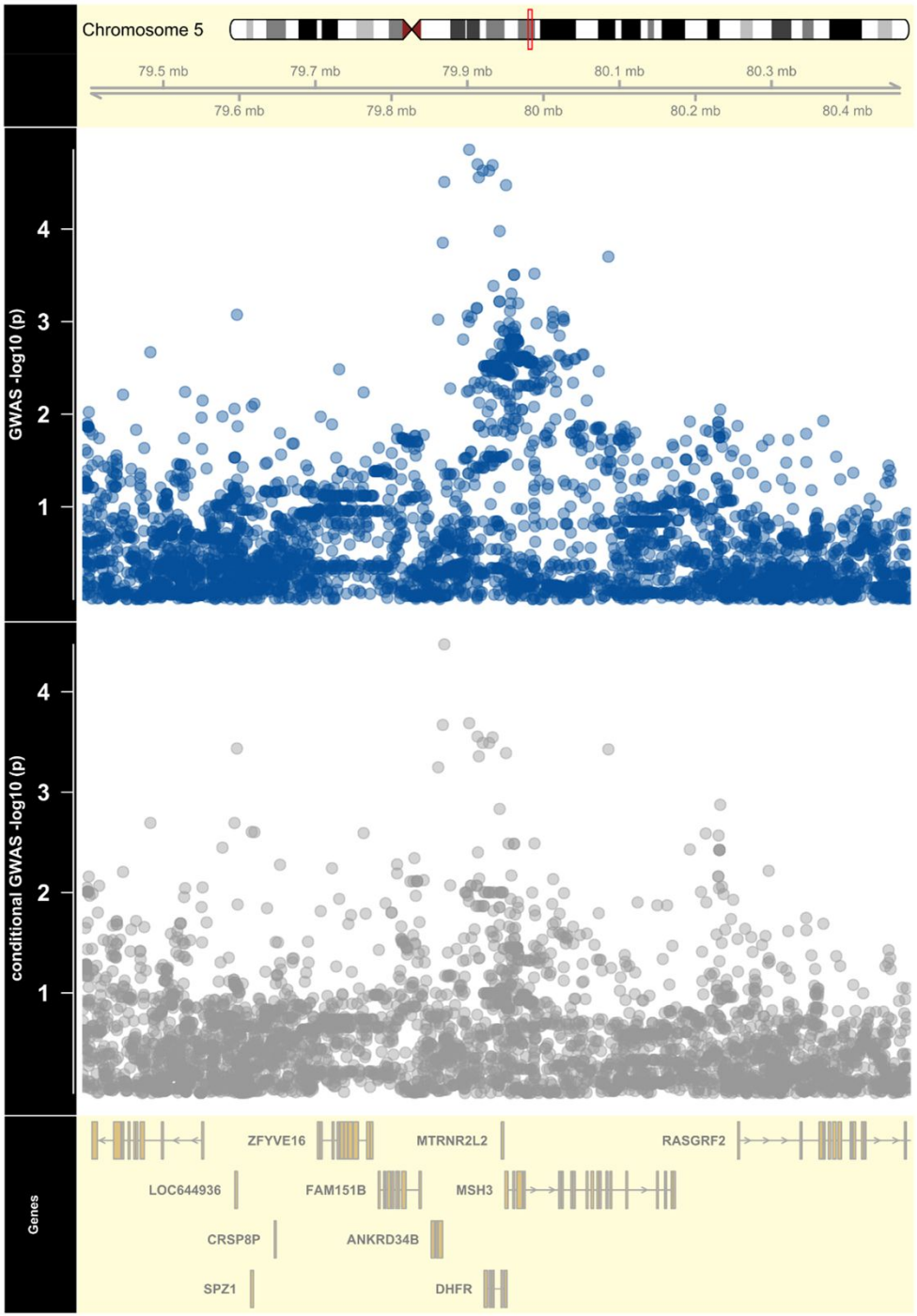


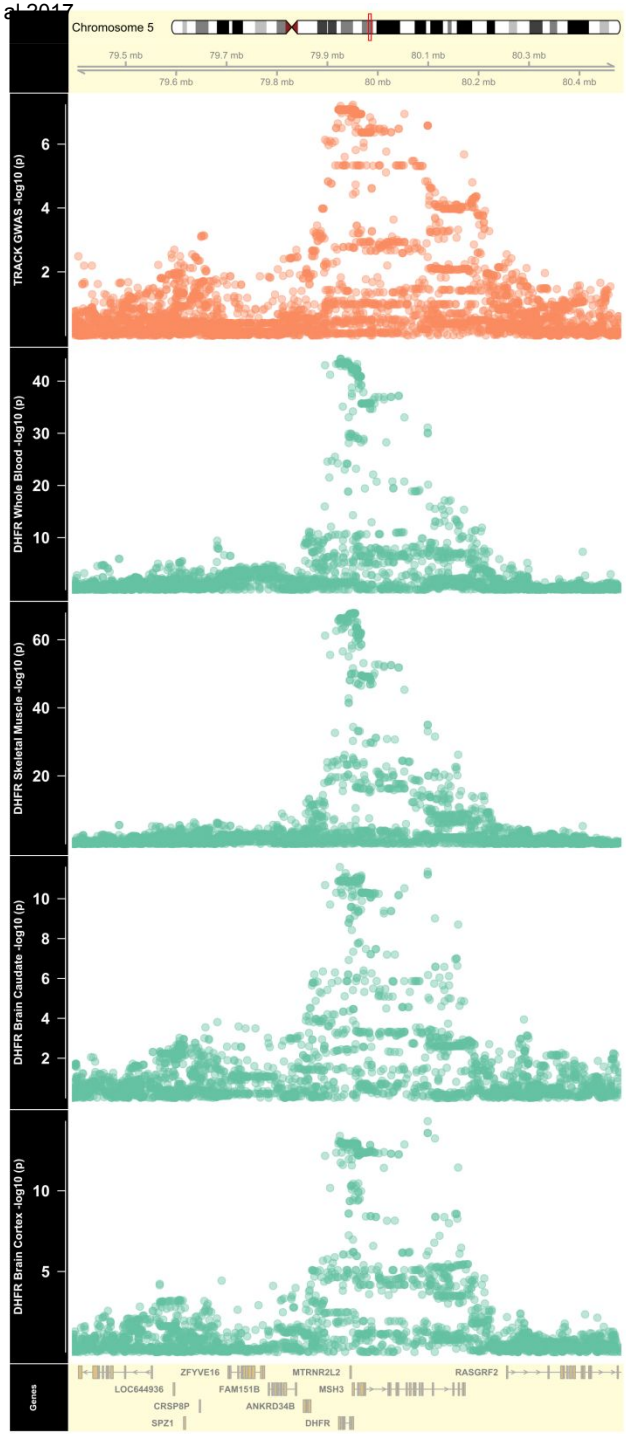
Supplementary Figure 4: Regional plot of TRACK-HD and REGISTRY meta-analysis GWAS signal in the MSH3-DHFR region before(top) and after (bottom) conditioning on the most significant SNP in the meta-analysis (rs1232027). The lack of significant association after conditioning on this SNP is consistent with here being only one association signal in the region.

Supplementary Figure 5: Regional plot of TRACK-HD and REGISTRY meta-analysis GWAS signal in the MSH3-DHFR region before(top) and after (bottom) conditioning on the most significant SNP in TRACK-HD (rs557874766). The lack of significant association after conditioning on this SNP is consistent with here being only one association signal in the region.



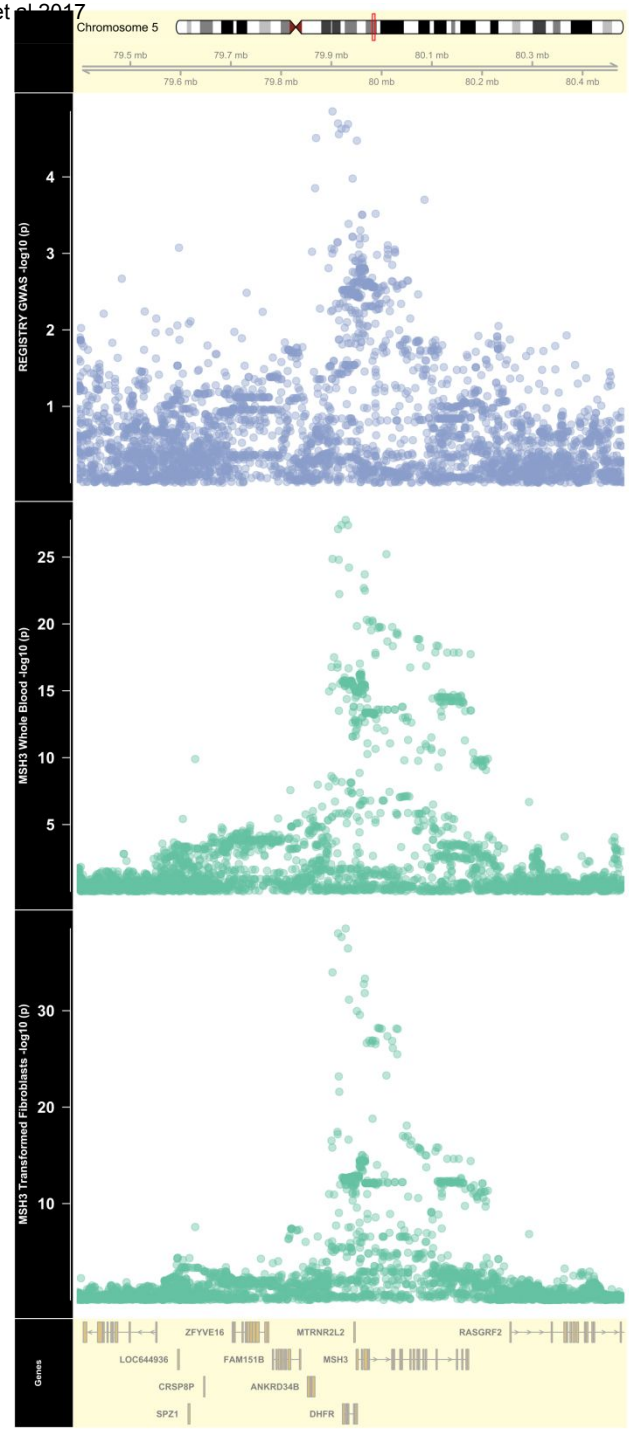
Supplementary Figure 6: Regional plot of REGISTRY GWAS signal in the MSH3-DHFR region before(top) and after (bottom) conditioning on the most significant SNP in TRACK-HD (rs557874766). The significance of association is largely unaffected by conditioning on this SNP. This indicates that rs557874766 does not explain the REGISTRY association signal in this region.



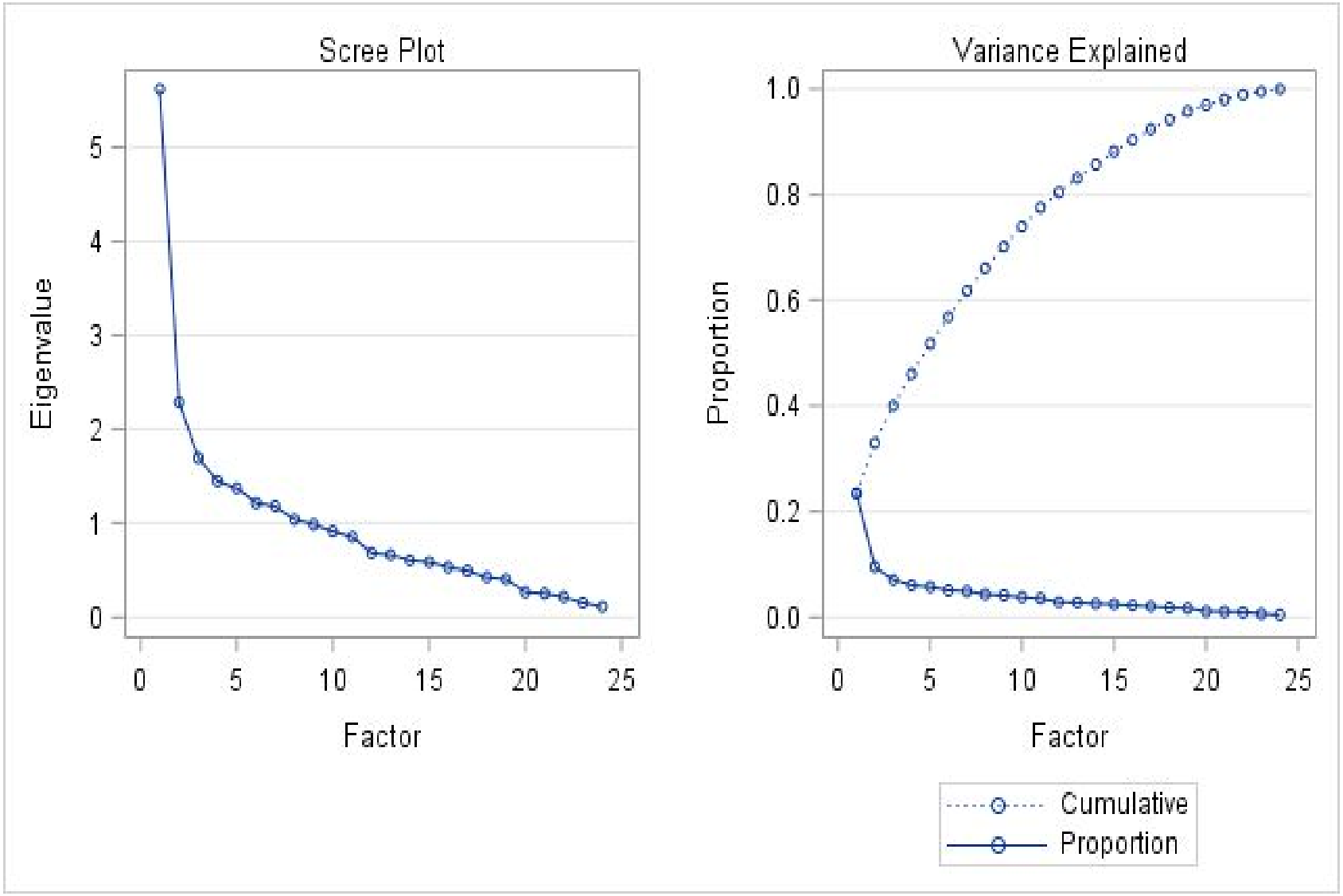


Supplementary Figure 7: Regional plot of TRACK-HD GWAS signal in the MSH3-DHFR region (top, red), along with GTeX eQTL associations with DHFR expression in (top-bottom) whole blood, skeletal muscle, cerebellum, cortex.

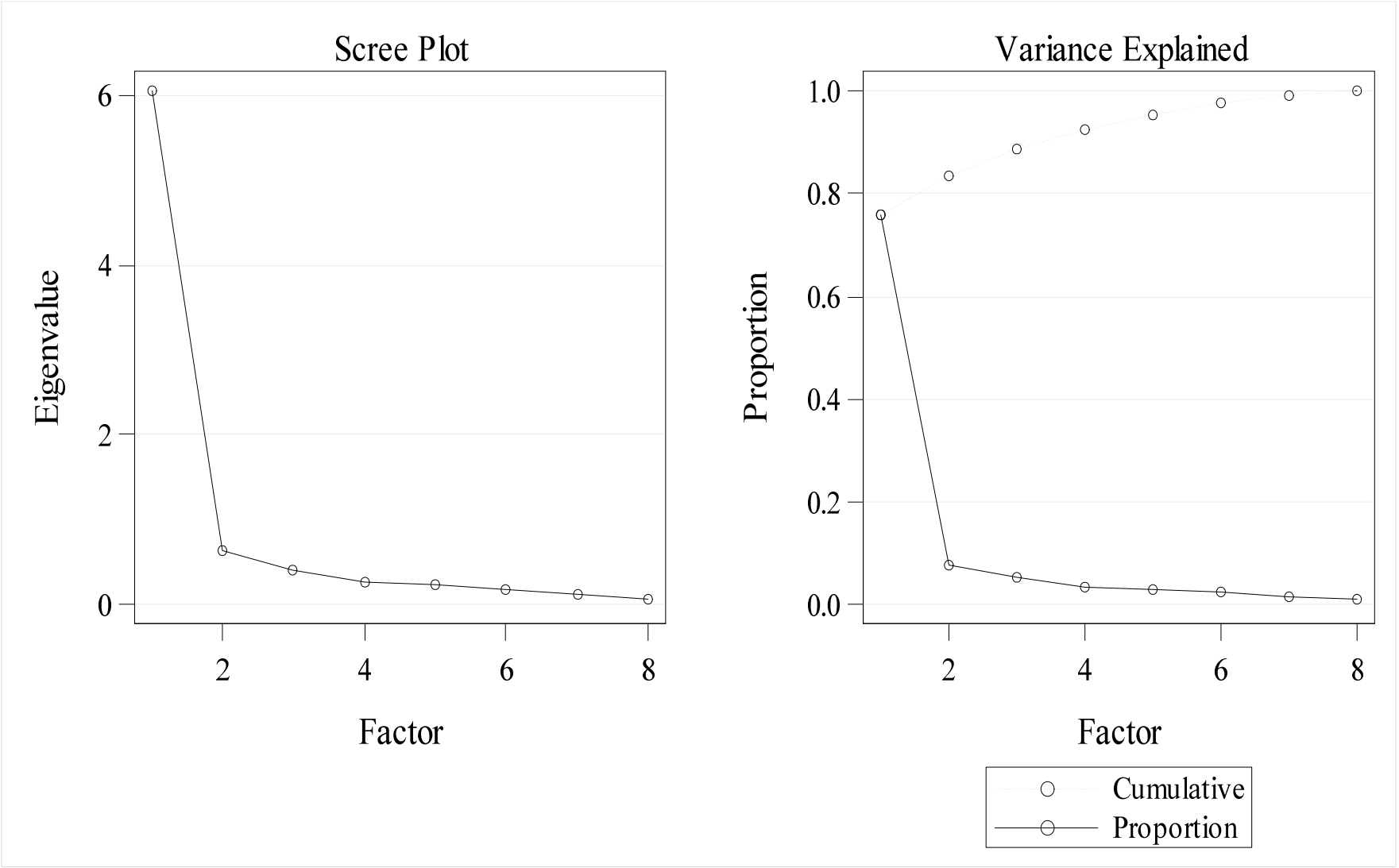
Supplementary Figure 8: Regional plot of REGISTRY GWAS signal in the MSH3-DHFR region (top, blue), along with GTeX eQTL associations with MSH3 expression in (top-bottom) whole blood, transformed fibroblasts.



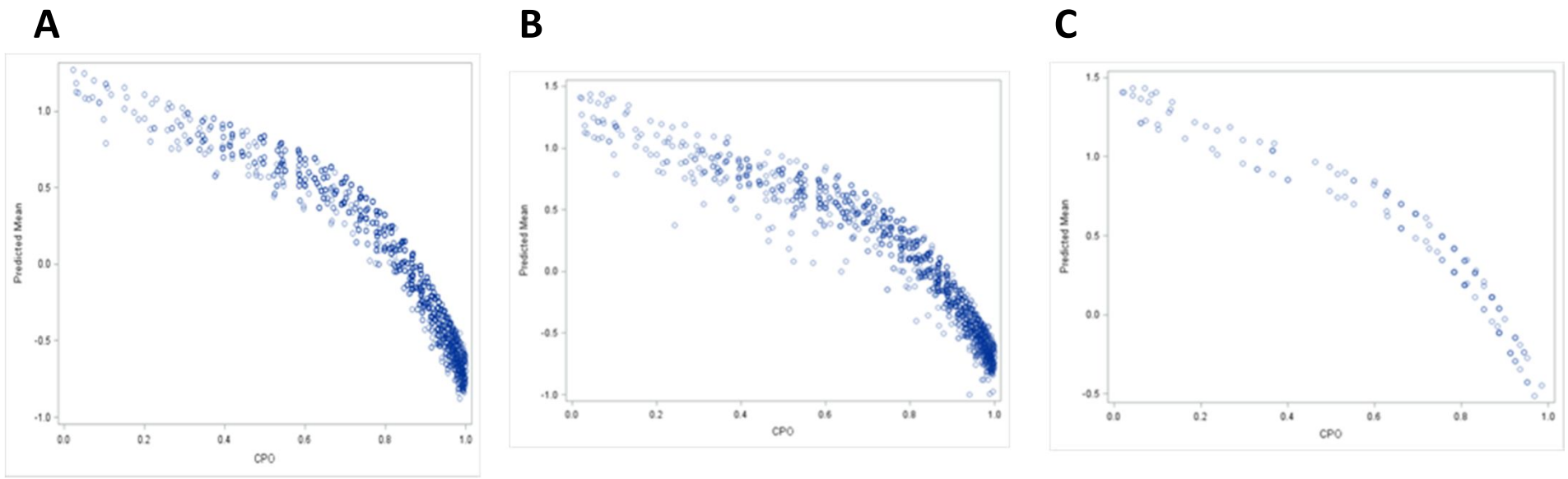
Supplementary Figure 9: (A) Scree Plot and (B) Plot showing proportion of variance explained in the TRACK-HD progression principal component analysis: the dominance of the first PC is illustrated.



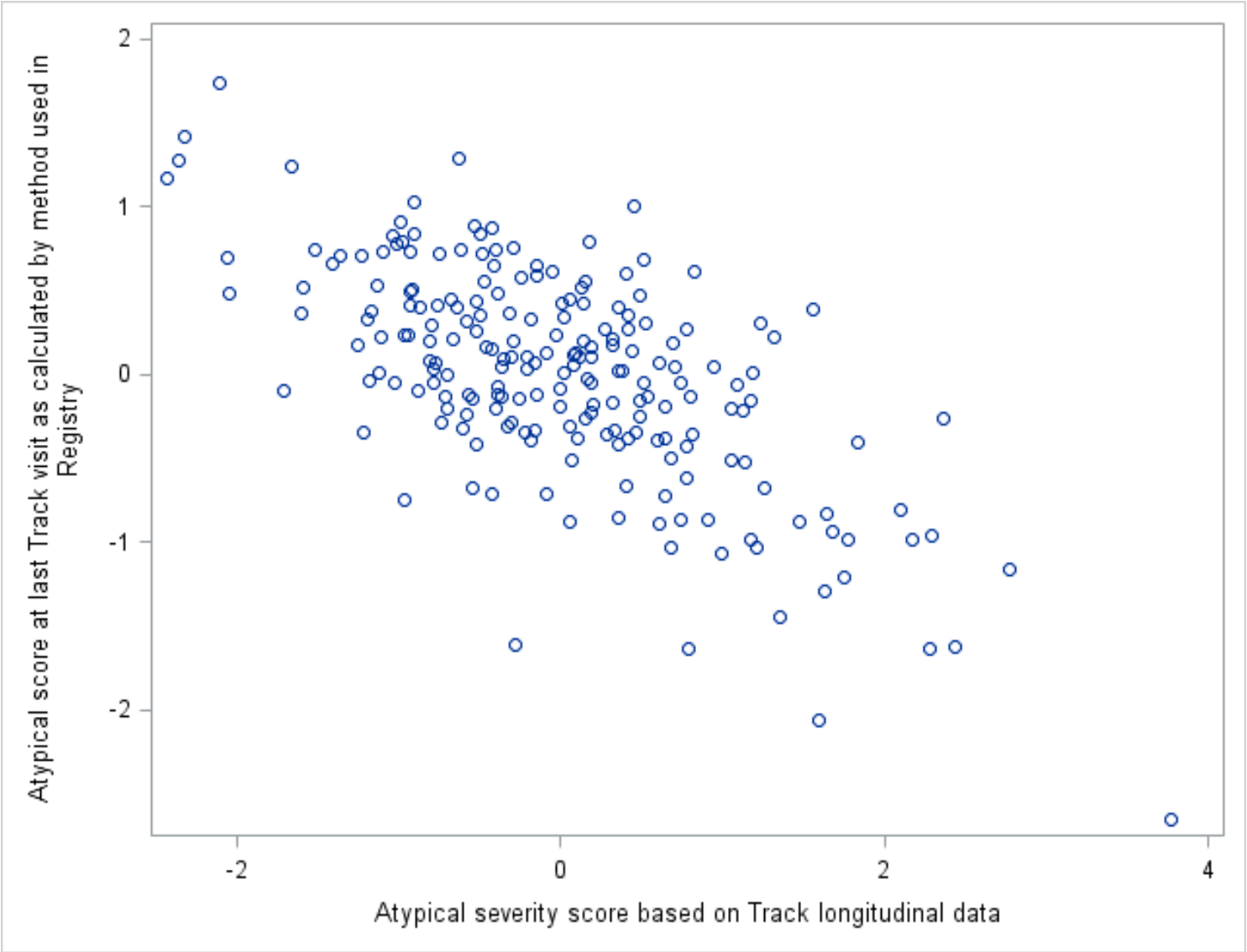
Supplementary Figure 10: (A) Scree Plot and (B) Plot showing proportion of variance explained in the REGISTRY progression principal component analysis: the dominance of the first PC is illustrated.



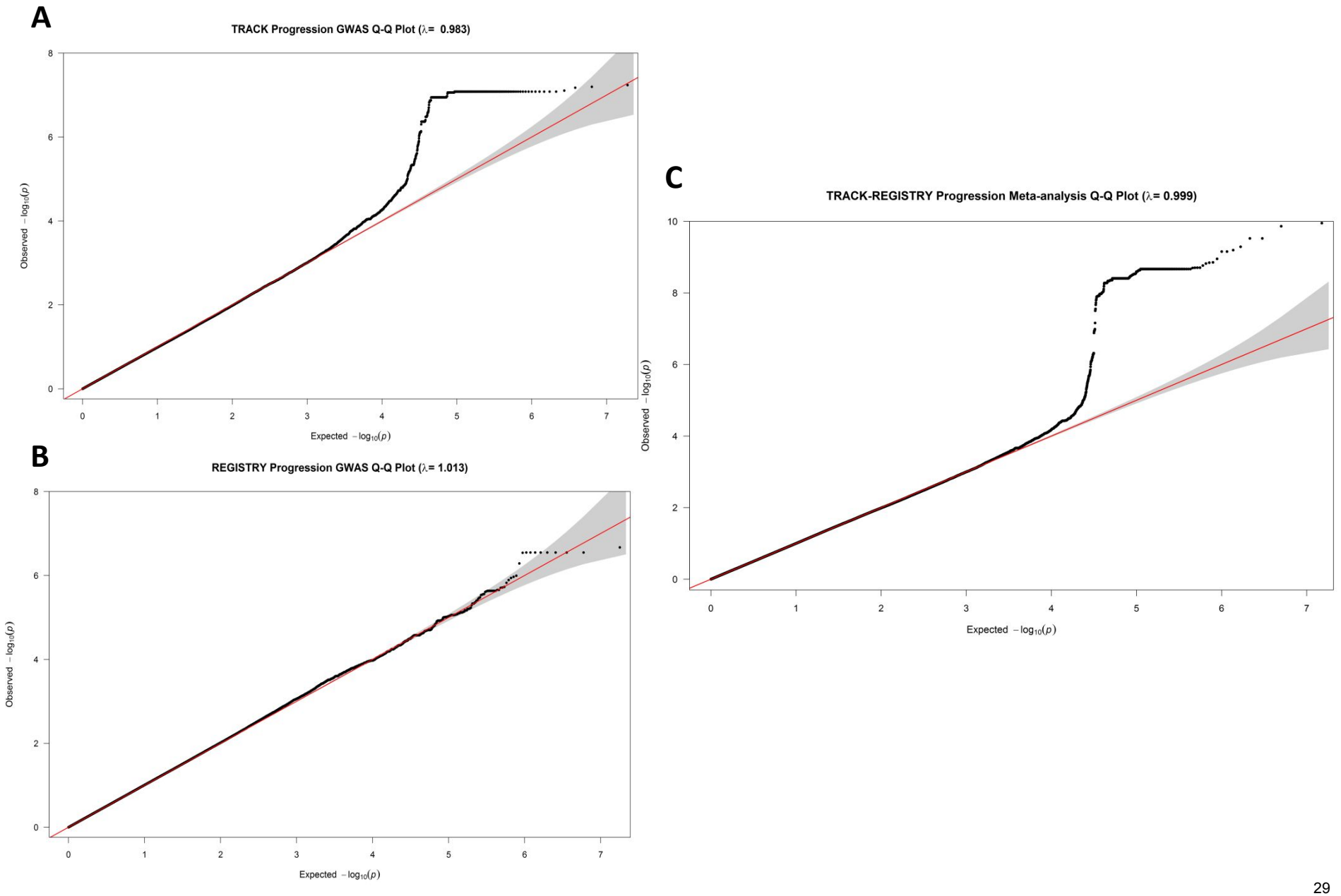
Supplementary Figure 11: Age-CAG severity function against clinical probability of onset (CPO) in REGISTRY. A: plot showing predicted values for all subjects. B: plot of predicted values using only subjects in the CAG 41– 55 range. C: Plot based on extrapolating the severity model to subjects with CAG in the 36-40 range (the appearance of two rather distinct lines are due to the gender effect, with women having lower predicted scores than men).



Supplementary Figure 12: Linear relationship between the longitudinal atypical severity scores used for the TRACK-HD analysis and cross-sectional atypical severity scores at the last TRACK visit when calculated using the method employed for the REGISTRY data (r = .674).



Supplementary Figure 13: QQ plots of the (A) TRACK-HD and (B) REGISTRY genome wide association studies. And (C) meta-analysis. λ close to 1 shows there is no systematic inflation of test statistics.



Supplementary tables:

Supplementary Table 1: Demographic details of TRACK-HD cohort. Further detail can be found in Tabrizi *et al* 2009, 2011, 2012, 2013.

	Number (female)	Age at baseline (years)	CAG repeat length
Manifest	122 (65)	48.0	43.5
Premanifest	96 (53)	40.6	43.0

Supplementary Table 2: List of Variables to be used in TRACK-HD progression analyses. Further detail regarding these measures can be found in Tabrizi *et al* 2009, 2011, 2012, 2013.

Symbol digit modality test (number correct)
Stroop word reading (number correct)
Paced Tapping 3 Hz (inverse std dev)
Spot the Change 5K
Emotion Recognition
Direct Circle (Log annulus length)
Indirect Circle (Log annulus length)
Total brain volume
Ventricular volume
Grey matter volume
White matter volume
Caudate volume
Metronome tapping, nondominant hand
Metronome tapping, nondominant hand
Speeded tapping, nondominant hand
Speeded tapping, nondominant hand
Speeded tapping, nondominant hand
Tongue force—heavy
Tongue force—light
Grip force, dom. hand, heavy condition
Grip force, dom. hand, heavy condition
Grip force, nondom. hand, heavy condition
Grip force, dom. hand, light condition
Grip force, nondom. hand, light condition

Supplementary Table 3: Correlations among Domain-Specific Residual Principal Components in the TRACK-HD analysis, showing that the first principle components of each domain are significantly correlated.

The prefaces "brain", "cog", and "mot" indicate the domain. The suffix f1, f2, etc, numbers the principal components within each domain. Having approximated the residual longitudinal variability within each of the three domains via principal components, we then examined cross-domain relationships among these components. For example, after accounting for CAG-age-risk, testing whether residual longitudinal change in the brain measures correlated with the Q-motor measures.

	brainf1	**brainf2**	**brainf3**	**cogf1**	**cogf2**	**cogf3**	**cogf4**	**motf1**	**motf2**	**motf3**	**motf4**
brainf1	1	0	0	**-0.355**	0.077	0.146	-0.068	**0.43**	0.096	-0.065	-0.139
p	*0*	*1*	*1*	***<.0001***	*0.26*	*0.03*	*0.32*	***<.0001***	*0.16*	*0.34*	*0.04*
brainf2	0	1	0	-0.097	-0.055	0.12	-0.016	0.005	-0.149	-0.043	0.041
p	*1*	*0*	*1*	*0.15*	*0.42*	*0.08*	*0.81*	*0.94*	*0.03*	*0.53*	*0.55*
brainf3	0	0	1	0.016	0.064	0.12	-0.009	0.15	0.05	-0.108	-0.161

p	*1*	*1*	*0*	*0.81*	*0.35*	*0.08*	*0.89*	*0.03*	*0.46*	*0.11*	*0.02*
cogf1				1	0	0	0	**-0.434**	-0.154	0.035	0.112
p				*0*	*1*	*1*	*1*	***<.0001***	*0.02*	*0.6*	*0.09*
cogf2				0	1	0	0	0.035	0.07	-0.12	-0.163
p				*1*	*0*	*1*	*1*	*0.59*	*0.29*	*0.07*	*0.01*
cogf3				0	0	1	0	0.105	-0.017	-0.092	-0.143
p				*1*	*1*	*0*	*1*	*0.11*	*0.8*	*0.16*	*0.03*
cogf4				0	0	0	1	-0.019	-0.05	-0.011	-0.054
p				*1*	*1*	*1*	*0*	*0.77*	*0.44*	*0.87*	*0.42*

Supplementary Table 4: PCA of Residual Longitudinal Change Among Variables form All 3 Domains in the TRACK-HD analysis showing that the variables that correlated with the domain specific analyses also correlated with the common principal component analysis.

Measure	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8
Symbol Digit	**-0.505**	-0.027	0.135	0.194	0.034	0.047	**-0.394**	-0.121
Stroop Word	**-0.391**	-0.017	0.361	**0.468**	0.078	-0.232	0.087	0.123
Paced Tapping 3 Hz (inverse std dev)	-0.054	-0.123	-0.031	-0.066	0.032	**0.621**	**-0.420**	0.233
Spot the Change 5K	0.224	-0.123	0.113	-0.223	-0.016	0.190	**0.427**	0.479
Emotion Recognition	-0.226	0.188	0.228	0.086	-0.090	**-0.415**	0.098	**0.264**
Direct Circle (Log annulus length)	-0.374	-0.101	**0.419**	0.199	**0.488**	0.258	0.060	-0.027
Indirect Circle (Log annulus length)	**-0.406**	-0.076	**0.407**	0.418	**0.161**	0.336	0.036	0.130
Total brain volume	**0.749**	**-0.457**	0.168	0.077	-0.046	-0.100	-0.115	-0.079
Ventricular volume	**-0.545**	**0.509**	-0.079	-0.125	0.094	0.131	0.274	0.043
Grey matter volume	**0.631**	**-0.491**	0.173	-0.050	-0.088	-0.137	0.038	-0.022
White matter volume	**0.699**	**-0.409**	0.252	-0.085	-0.019	-0.048	0.062	0.044
Caudate volume	**0.584**	**-0.426**	0.082	0.223	0.086	0.083	-0.055	0.046
Metronome tapping, nondominant hand	**0.433**	-0.033	-0.206	-0.338	0.104	0.392	0.037	-0.081
(log of tap initiation SD for all trials)	**0.433**	-0.033	-0.206	-0.338	0.104	0.392	0.037	-0.081
Metronome tapping, nondominant hand (inv tap initiation SD for self-paced trials)	-0.033	-0.212	0.013	0.144	0.116	0.133	0.347	**-0.705**
Speeded tapping, nondominant hand (log of repetition time SD)	0.380	-0.022	**-0.483**	0.315	**0.554**	-0.206	-0.058	0.123
Speeded tapping, nondominant hand (log of tap duration SD)	**0.594**	0.028	-0.335	0.182	**0.437**	-0.061	0.027	0.206
Speeded tapping, nondominant hand (mean intertap time)	0.316	0.373	-0.219	0.006	**0.411**	-0.036	-0.002	-0.120
Tongue force—heavy (log coefficient of variation)	0.147	0.016	-0.332	**0.586**	**-0.445**	0.177	-0.033	0.012
Tongue force—light (log coefficient of variation)	0.247	0.114	-0.399	**0.451**	**-0.407**	0.191	0.217	0.066
Grip force, dom. hand, heavy condition (log of mean orientation)	0.615	**0.488**	0.252	0.009	-0.078	-0.014	-0.336	-0.077
Grip force, dom. hand, heavy condition (log of mean position)	**0.568**	**0.518**	0.207	0.033	-0.027	-0.051	-0.381	-0.042
Grip force, nondom. hand, heavy condition (log of coefficient of variation)	**0.516**	**0.400**	0.213	0.108	0.003	0.122	0.231	-0.145
Grip force, dom. hand, light condition (log of coefficient of variation)	**0.681**	0.311	0.250	0.034	0.016	0.140	0.188	0.114
Grip force, nondom. hand, light condition (log of coefficient of variation)	**0.647**	**0.430**	0.293	0.071	-0.061	0.071	0.163	-0.055
Pct Variance Explained	***23.4***	***9.5***	***7.1***	***6***	***5.7***	***5.1***	***4.9***	***4.3***

Supplementary Table 5: Factor pattern of the first two principal component analysis of the REGISTRY severity score which was used as a progression score for the Registry data. Factor 1 = 1st PC; Factor 2 = 2nd PC.

		Factor Pattern	
Variable	**Variable explanation**	**Factor1**	**Factor2**
sqrtmotor	Square root of the UHDRS total motor score	-0.84233	0.30062
verfl	UHDRS verbal fluency	0.79108	0.24136
sdmt	UHDRS symbol digit score	0.89833	0.1522
scnt	UHDRS Stroop color naming	0.89596	0.25872
swrt	UHDRS Stroop word reading	0.88978	0.2109
sit1	UHDRS Stroop interference score	0.87684	0.21789
tfc	UHDRS total functional capacity	0.8746	-0.39367
fasscore	UHDRS functional assessment scale	0.88355	-0.38555

Supplementary Table 6: Independent association signals from the TRACK-HD Progression GWAS (at p-value < 10-5)

Chromosome	Start (BP)	End (BP)	Index SNP (dbSNP b146)	Reference Allele (A1)	Alternate Allele (A2)	Minor Allele Frequency (MAF)	INFO score	Beta	Standard Error	P-value	Number of SNPs	Length (KB)	Gene(s) tagged (+/- 20 KB)
5	79895438	80196258	rs557874766	G	C	0.238	1.000	-0.581	0.107	5.80E-08	380	300.82	DHFR, MSH3, MTRNR2L2
4	74064920	74362359	rs16849472	T	C	0.019	1.000	1.677	0.318	1.34E-07	10	297.44	AFM, AFP, ALB, ANKRD17, LOC728040
3	20860340	20919615	rs111902872	T	C	0.012	0.920	2.419	0.460	1.47E-07	2	59.276	*none*
1	239493679	239917976	rs115206404	A	G	0.009	0.805	2.598	0.503	2.46E-07	2	424.3	CHRM3, CHRM3-AS2
13	89829918	89856005	rs546753686	A	G	0.009	0.949	2.610	0.506	2.50E-07	2	26.088	*none*
6	31892827	31895971	rs188144048	G	C	0.016	1.000	-1.923	0.380	4.30E-07	2	3.145	C2, CFB, LOC102060414
4	52815077	52815077	rs151302971	C	T	0.060	0.998	0.963	0.192	4.98E-07	1	0.001	*none*
10	132818509	132881313	rs150136271	T	C	0.007	0.845	2.881	0.582	7.38E-07	3	62.805	TCERG1L
8	128074135	128092501	rs76712904	T	A	0.009	1.000	2.532	0.512	7.68E-07	13	18.367	PCAT2, PRNCR1
6	147033320	147049507	rs76605780	G	A	0.009	1.000	2.524	0.512	8.42E-07	4	16.188	ADGB
10	24684087	24684087	rs55795540	A	C	0.065	0.995	0.919	0.187	8.85E-07	1	0.001	KIAA1217
22	41330451	41572210	rs185116512	T	C	0.009	0.998	2.482	0.506	9.51E-07	2	241.76	EP300, EP300-AS1, MIR1281, RBX1, XPNPEP3
6	32537468	33038283	rs1062481	T	C	0.009	1.000	2.477	0.512	1.33E-06	6	500.82	BRD2, HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DRB1, HLA-DRB6, LOC100294145, PSMB8, PSMB9, TAP1, TAP2, TAPSAR1
11	125957124	126008830	rs200669142	A	AT	0.012	0.999	2.177	0.452	1.44E-06	3	51.707	*none*
2	67244370	67346420	rs56349456	A	G	0.032	0.992	1.334	0.277	1.50E-06	13	102.05	LOC644838, LOC102800447
4	141111891	141111891	rs57282598	G	A	0.009	0.985	2.453	0.510	1.50E-06	1	0.001	*none*

11	4521374	4879985	rs117945252	G	C	0.012	0.840	2.188	0.456	1.60E-06	3	358.61	C11orf40, OR51D1, OR51E1, OR51E2, OR51F1, OR51F2, OR51S1, OR52I1, OR52I2, OR52K1, OR52M1, OR52R1, TRIM68
11	6750653	6917038	rs3889139	A	G	0.007	0.972	2.795	0.584	1.67E-06	4	166.39	GVINP1, OR2AG1, OR2AG2, OR2D2, OR6A2, OR10A2, OR10A4, OR10A5
5	128287222	128679437	rs146180907	T	C	0.009	0.999	2.405	0.505	1.93E-06	6	392.22	ISOC1, MIR4633, SLC27A6
14	78805174	78901796	rs117746737	G	A	0.044	0.860	1.152	0.243	2.10E-06	9	96.623	NRXN3
2	58253090	58774645	rs146045300	G	A	0.009	0.999	1.940	0.412	2.46E-06	5	521.56	FANCL, LINC01122, VRK2
3	36891939	36956117	rs146080846	ATTAT	A	0.014	0.953	1.965	0.418	2.54E-06	2	64.179	TRANK1
19	6675794	6675794	rs183566601	G	C	0.012	0.908	2.139	0.455	2.56E-06	1	0.001	C3, TNFSF14
1	74500787	74665215	rs75274216	G	C	0.016	1.000	1.551	0.331	2.77E-06	2	164.43	FPGT, FPGT-TNNI3K, LRRIQ3
8	58860626	58860626	rs577181066	T	C	0.009	1.000	-2.314	0.495	3.00E-06	1	0.001	*none*
7	153670448	153672048	rs39153	T	A	0.035	1.000	1.264	0.272	3.23E-06	6	1.601	DPP6
9	107972517	107982792	rs33922537	TA	T	0.088	0.991	0.813	0.175	3.25E-06	44	10.276	*none*
2	182396359	182396359	rs185077546	A	G	0.009	1.000	2.344	0.504	3.28E-06	1	0.001	CERKL, ITGA4
2	131955255	132160922	rs377754762	C	G	0.009	0.971	2.342	0.504	3.44E-06	3	205.67	LINC01120, LOC440910, POTEE, WTH3DI
7	37980409	37980409	rs7798464	C	T	0.478	0.999	-0.515	0.111	3.48E-06	1	0.001	EPDR1
6	136578804	136578804	rs182174986	C	T	0.007	1.000	2.694	0.582	3.70E-06	1	0.001	BCLAF1, MTFR2
1	10849645	10849645	rs10864471	G	A	0.076	0.996	0.798	0.173	3.85E-06	1	0.001	CASZ1
16	84533672	85735002	rs544820106	T	C	0.007	0.998	2.692	0.583	3.90E-06	3	1201.3	C16orf74, COTL1, CRISPLD2, FAM92B, GINS2, GSE1, KIAA0513, KLHL36, LINC00311, LOC400548, MIR5093, MIR7851, TLDC1, USP10, ZDHHC7
9	140124101	140326510	rs576074352	T	C	0.009	1.000	2.320	0.505	4.26E-06	3	202.41	C9orf169, C9orf173, ENTPD8, EXD3, FAM166A, LOC100129722, MIR7114, NDOR1, NELFB, NOXA1, NRARP, NSMF, RNF208, RNF224, SLC34A3, TOR4A, TUBB4B
3	147917	147917	rs190854428	T	C	0.014	0.990	1.920	0.418	4.29E-06	1	0.001	*none*
7	20723109	20725291	rs78036476	G	T	0.024	1.000	1.515	0.330	4.44E-06	2	2.183	ABCB5
10	6409502	6409502	rs7915166	C	T	0.308	1.000	0.496	0.108	4.80E-06	1	0.001	*none*
4	178648851	178648851	rs191350537	A	G	0.014	0.999	1.882	0.413	5.15E-06	1	0.001	LINC01098
2	121177685	121177685	rs542948395	T	C	0.009	1.000	2.291	0.504	5.37E-06	1	0.001	*none*
19	40114782	40248603	rs544526021	T	G	0.009	1.000	2.301	0.506	5.42E-06	3	133.82	CLC, LEUTX, LGALS13, LGALS14, LGALS16, LGALS17A, LOC100129935
8	15256069	15266930	rs11203702	A	T	0.118	0.99	0.680	0.15	5.56E-	3	10.8	*none*

							6		0	06		62	
7	126436990	126497288	rs139456699	A	G	0.019	1.000	-1.608	0.354	5.74E-06	3	60.299	GRM8
4	144227742	144227742	rs185067403	A	G	0.009	1.000	2.294	0.506	5.80E-06	1	0.001	*none*
13	20224902	20377448	rs35231784	GC	G	0.260	0.995	-0.495	0.110	6.11E-06	36	152.55	MPHOSPH8, PSPC1
3	71536485	71536485	rs139096029	A	G	0.019	1.000	1.603	0.355	6.26E-06	1	0.001	FOXP1
2	6216990	6265656	rs13017659	A	C	0.068	0.975	0.818	0.181	6.28E-06	4	48.667	*none*
8	141293251	141293251	rs186776689	T	C	0.009	1.000	2.277	0.504	6.30E-06	1	0.001	TRAPPC9
6	117738434	117812254	rs143087465	T	C	0.009	1.000	2.289	0.507	6.42E-06	3	73.821	DCBLD1, ROS1
1	71806741	71806741	rs615589	C	T	0.017	0.953	1.772	0.393	6.45E-06	1	0.001	*none*
1	34835613	34886817	rs10753307	C	G	0.146	1.000	0.646	0.144	6.94E-06	35	51.205	*none*
13	73610584	73624638	rs13378884	G	A	0.280	1.000	0.500	0.111	7.28E-06	2	14.055	KLF5, PIBF1
3	21479214	21521820	rs73045437	A	G	0.131	0.996	0.683	0.152	7.32E-06	2	42.607	ZNF385D
6	24188337	24301530	rs138968896	A	C	0.047	0.998	1.058	0.236	7.39E-06	21	113.19	DCDC2
18	64640322	64640322	rs11663556	T	C	0.009	0.997	2.246	0.505	8.55E-06	1	0.001	*none*
16	21651427	21706726	rs139057628	C	T	0.012	0.881	1.999	0.452	9.82E-06	2	55.3	IGSF6, METTL9, OTOA
11	122679684	122679684	rs5795348	G	GA	0.201	0.987	0.587	0.133	9.91E-06	1	0.001	UBASH3B
10	51520713	51520713	rs74922941	C	T	0.016	1.000	1.701	0.385	9.92E-06	1	0.001	TIMM23B

Supplementary Table 7: Independent association signals from the meta-analysis of TRACK-HD and REGISTRY Progression GWAS (at p-value < 10-5)

Index SNP	P-value	Clump coordinates	Clump size (KB)	Gene(s) tagged
rs1232027	1.12E-10	chr5:79895438..80198404	302.967	DHFR, MSH3, MTRNR2L2
rs73786719	8.53E-07	chr6:147034576..147037984	3.409	ADGB
rs114688092	1.51E-06	chr3:47026101..47315538	289.438	CCDC12, KIF9, KIF9-AS1, KLHL18, NBEAL2, NRADDP, SETD2
rs79029191	1.67E-06	chr18:8053863..8080538	26.676	PTPRM
rs932428	1.79E-06	chr20:37518361..37876772	358.412	DHX35, FAM83D, LOC339568, PPP1R16B
rs3889139	2.13E-06	chr11:6885429..6917038	31.61	OR2D2, OR10A2, OR10A4, OR10A5
rs114643193	2.65E-06	chr4:2844682..2939191	94.51	ADD1, MFSD10, NOP14, NOP14-AS1, SH3BP2
rs6882169	2.72E-06	chr5:167668230..167668230	0.001	CTB-178M22.2, TENM2
rs80260687	2.92E-06	chr8:97232364..97304966	72.603	MTERFD1, PTDSS1, UQCRB
rs28406206	3.13E-06	chr14:105680474..105688082	7.609	BRF1
rs4736525	3.37E-06	chr8:132924474..133030989	106.516	EFR3A, OC90
rs78621558	4.44E-06	chr5:80012735..80012735	0.001	MSH3
rs72715653	4.80E-06	chr4:178641337..178730329	88.993	LINC01098, LINC01099
rs4720024	4.94E-06	chr7:30941255..30942312	1.058	AQP1, FAM188B, INMT-FAM188B
rs117933444	5.75E-06	chr6:167362873..167410443	47.571	FGFR1OP, MIR3939, RNASET2
rs116220136	5.82E-06	chr5:23353255..23436446	83.192	*none*
rs8031584	8.15E-06	chr15:31185616..31292023	106.408	FAN1, MTMR10, TRPM1
rs3013648	9.10E-06	chr13:85296644..85374146	77.503	*none*
rs11197481	9.12E-06	chr10:117708803..117708803	0.001	ATRNL1
rs117440785	9.15E-06	chr10:17411451..17531334	119.884	ST8SIA6, ST8SIA6-AS1
rs111258354	9.87E-06	chr2:60823224..60883232	60.009	*none*

Supplementary Table 8: Co-localisation between TRACK-HD GWAS signal on chromosome 5 and GTeX eQTLs for MSH3, DHFR

Dataset	Dataset source	Most significant eQTL p-value	N Overlapping SNPs	COLOC probability (of shared variants)
MSH3 (Blood)	GTEx	1.70E-28	647	1.76%
MSH3 (Fibroblasts)	GTEx	3.10E-39	646	1.76%

MSH3 (Cerebellum)	GTEx	1.10E-06	592	8.83%
MSH3 (Caudate)	GTEx	1.65E-05	588	25.20%
MSH3 (Cortex)	GTEx	5.53E-05	582	53.10%
DHFR (Blood)	GTEx	5.20E-45	647	98.10%
DHFR (Skeletal muscle)	GTEx	1.30E-68	655	99.20%
DHFR (Cerebellum)	GTEx	7.60E-13	592	28.30%
DHFR (Caudate)	GTEx	2.60E-12	588	99.00%
DHFR (Cortex)	GTEx	4.90E-15	582	96.10%

Supplementary Table 9: Co-localisation between REGISTRY GWAS signal on chromosome 5 and GTeX eQTLs for MSH3, DHFR

Dataset	Dataset source	Most significant eQTL p-value	N Common SNPs	COLOC probability (of shared variants)
MSH3 (Blood)	GTEx	1.70E-28	3289	97.80%
MSH3 (Fibroblasts)	GTEx	3.10E-39	3224	97.80%
MSH3 (Cerebellum)	GTEx	1.10E-06	2888	12.50%
MSH3 (Caudate)	GTEx	1.65E-05	2866	10.40%
MSH3 (Cortex)	GTEx	5.53E-05	2853	23.10%
DHFR (Blood)	GTEx	5.20E-45	3289	36.40%
DHFR (Skeletal muscle)	GTEx	1.30E-68	3336	34.10%
DHFR (Cerebellum)	GTEx	7.60E-13	2888	0.88%
DHFR (Caudate)	GTEx	2.60E-12	2866	43.30%
DHFR (Cortex)	GTEx	4.90E-15	2853	23.10%

Supplementary Table 10: Co-localisation between TRACK-HD GWAS signal on chromosome 5 and GTeX eQTLs for MSH3, DHFR

Dataset	Dataset source	Most significant eQTL p-value	N Overlapping SNPs	COLOC probability (of shared variants)
MSH3 (Blood)	GTEx	1.70E-28	647	1.76%
MSH3 (Fibroblasts)	GTEx	3.10E-39	646	1.76%
MSH3 (Cerebellum)	GTEx	1.10E-06	592	8.83%
MSH3 (Caudate)	GTEx	1.65E-05	588	25.20%
MSH3 (Cortex)	GTEx	5.53E-05	582	53.10%
DHFR (Blood)	GTEx	5.20E-45	647	98.10%
DHFR (Skeletal muscle)	GTEx	1.30E-68	655	99.20%
DHFR (Cerebellum)	GTEx	7.60E-13	592	28.30%
DHFR (Caudate)	GTEx	2.60E-12	588	99.00%
DHFR (Cortex)	GTEx	4.90E-15	582	96.10%

Supplementary Table 11: Independent association signals from the REGISTRY Progression GWAS (at p-value < 10-5)

Chromosome	Start (BP)	End (BP)	Index SNP (dbSNP b146)	Reference Allele (A1)	Alternate Allele (A2)	Minor Allele Frequency (MAF)	INFO score	Beta	Standard Error	P-value	Number of SNPs	Length (KB)	Gene(s) tagged (+/- 20 KB)
10	117708803	117708803	rs11197481	A	G	0.176	0.997	0.193	0.037	2.14E-07	1	0.001	ATRNL1
15	30996093	31314317	rs10611148	A	AAGTT	0.274	0.999	0.160	0.031	2.84E-07	72	318.225	FAN1, HERC2P10, LOC100288637, MTMR10, TRPM1
6	67807895	67905502	rs75695330	C	T	0.268	0.522	0.176	0.034	2.88E-07	12	97.608	*none*

12	117967637	117989548	rs10774933	C	T	0.197	0.992	0.171	0.035	1.08E-06	10	21.912	KSR2
3	86317394	86321260	rs78656706	A	G	0.025	0.610	-0.440	0.091	1.15E-06	2	3.867	*none*
1	151576174	151614297	rs761712980	A	AATAAAT	0.089	0.858	-0.231	0.049	2.21E-06	3	38.124	SNX27
3	93566149	93725515	rs62266135	T	G	0.015	0.500	0.542	0.116	2.77E-06	2	159.367	ARL13B, PROS1, STX19
5	23353255	23436446	rs72754785	G	A	0.045	0.908	0.316	0.067	2.87E-06	4	83.192	*none*
5	36704641	36954077	rs62356368	T	G	0.016	0.985	0.531	0.114	2.92E-06	4	249.437	LOC646719, NIPBL, SLC1A3
20	13209795	13245958	rs759901416	T	TCTCTT	0.156	0.857	0.183	0.039	3.33E-06	3	36.164	ISM1, ISM1-AS1
10	6403262	6407737	rs2387399	T	C	0.358	0.997	0.136	0.029	3.42E-06	2	4.476	*none*
14	33262946	33284981	rs991550	G	A	0.077	0.996	-0.248	0.054	3.60E-06	3	22.036	AKAP6
10	85432343	85432343	rs140550510	G	C	0.014	0.849	0.549	0.119	4.00E-06	1	0.001	*none*
15	92882676	92897269	rs145271683	T	C	0.021	0.908	-0.450	0.098	4.65E-06	4	14.594	*none*
4	3860844	3863228	rs28501173	T	G	0.270	0.997	0.145	0.032	4.66E-06	15	2.385	*none*
12	117075057	117079318	rs144854396	T	TC	0.331	0.890	0.135	0.030	6.01E-06	8	4.262	*none*
16	6945437	6945437	rs188738316	A	G	0.118	0.652	0.205	0.045	6.22E-06	1	0.001	RBFOX1
5	81062170	81062170	rs4703843	G	T	0.165	0.915	0.172	0.038	6.27E-06	1	0.001	SSBP2
11	62532798	62614506	rs41542313	T	C	0.031	0.999	0.367	0.081	6.31E-06	3	81.709	MIR6514, MIR6748, NXF1, POLR2G, SLC3A2, SNHG1, SNORD22, SNORD25, SNORD26, SNORD27, SNORD28, SNORD29, SNORD30, SNORD31, STX5, TAF6L, TMEM179B, TMEM223, WDR74, ZBTB3
21	45715620	45734831	rs3746965	A	G	0.235	1.000	0.150	0.033	6.75E-06	4	19.212	AIRE, C21orf2, PFKL

3	49451639	52028491	rs28587738	A	C	0.014	0.563	0.555	0.124	7.54E-06	5	2576.85	ABHD14A, ABHD14A-ACY1, ABHD14B, ACY1, AMIGO3, AMT, APEH, BSN, BSN-AS2, C3orf18, CACNA2D2, CAMKV, CDHR4, CISH, CYB561D2, DAG1, DOCK3, FAM212A, GMPPB, GNAI2, GNAT1, GPR62, GRM2, HEMK1, HYAL1, HYAL2, HYAL3, IFRD2, IP6K1, IQCF1, IQCF2, IQCF3, IQCF4, IQCF5, IQCF5-AS1, IQCF6, LSMEM2, MANF, MAPKAPK3, MIR4787, MIR5193, MIR5787, MIR6872, MON1A, MST1, MST1R, NAT6, NICN1, NPRL2, PARP3, PCBP4, RAD54L2, RASSF1, RASSF1-AS1, RBM5, RBM5-AS1, RBM6, RBM15B, RHOA, RNF123, RPL29, RRP9, SEMA3B, SEMA3B-AS1, SEMA3F, SLC38A3, TCTA, TEX264, TMEM115, TRAIP, TUSC2, UBA7, VPRBP, ZMYND10
15	31126401	31276476	rs7180337	G	T	0.020	0.621	-0.442	0.099	7.77E-06	22	150.076	FAN1, HERC2P10, MTMR10, TRPM1
15	31345498	31367837	rs28632121	C	T	0.247	0.998	-0.144	0.032	7.96E-06	8	22.34	MIR211, TRPM1
5	158949420	158950938	rs115553365	G	T	0.020	0.799	0.450	0.101	8.58E-06	2	1.519	*none*
19	17164401	17164401	rs73022346	T	G	0.013	0.649	-0.550	0.124	8.93E-06	1	0.001	HAUS8
7	70111666	70238809	rs80237739	C	T	0.025	0.850	-0.405	0.092	9.80E-06	4	127.144	AUTS2

Supplementary Table 12: Gene-wide p-values in TRACK-HD, REGISTRY, the TRACK-REGISTRY meta-analysis and GeM for all genes in the top 14 pathways from GeM

Pathway	Entrez	Gene Symbol	Chr	Start	End	p(TRACK)	p(REGISTRY)	p(META)	p(GeM)	Description
GO:32300	4437	MSH3	5	79950467	80172634	2.94E-08	9.52E-04	8.88E-11	2.03E-02	mismatch repair complex
GO:30983	4437	MSH3	5	79950467	80172634	2.94E-08	9.52E-04	8.88E-11	2.03E-02	mismatched DNA binding
GO:6298	4437	MSH3	5	79950467	80172634	2.94E-08	9.52E-04	8.88E-11	2.03E-02	mismatch repair
KEGG 3430	4437	MSH3	5	79950467	80172634	2.94E-08	9.52E-04	8.88E-11	2.03E-02	KEGG_MISMATCH_REPAIR
KEGG 3430	5425	POLD2	7	44154279	44163169	7.21E-04	3.12E-01	2.75E-03	5.20E-01	KEGG_MISMATCH_REPAIR
KEGG 3430	3978	LIG1	19	48618703	48673560	1.65E-02	8.28E-02	5.35E-04	6.51E-02	KEGG_MISMATCH_REPAIR
KEGG 3430	27030	MLH3	14	75480467	75518235	1.69E-02	6.69E-01	1.47E-01	6.59E-03	KEGG_MISMATCH_REPAIR
GO:6298	27030	MLH3	14	75480467	75518235	1.69E-02	6.69E-01	1.47E-01	6.59E-03	mismatch repair
GO:32407	27030	MLH3	14	75480467	75518235	1.69E-02	6.69E-01	1.47E-01	6.59E-03	MutSalpha complex binding
GO:32300	27030	MLH3	14	75480467	75518235	1.69E-02	6.69E-01	1.47E-01	6.59E-03	mismatch repair complex
GO:30983	27030	MLH3	14	75480467	75518235	1.69E-02	6.69E-01	1.47E-01	6.59E-03	mismatched DNA binding
GO:10822	5534	PPP3R1	2	68405989	68479651	1.82E-02	4.76E-01	6.12E-01	8.40E-01	positive regulation of mitochondrion organization

GO: 33683	2068	ERCC2	19	45854649	45873845	2.03E-02	8.83E-01	3.45E-01	7.45E-01	nucleotide-excision repair, DNA incision
GO: 90200	84334	APOPT1	14	104029299	104057236	2.51E-02	8.19E-01	4.40E-01	8.18E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	84334	APOPT1	14	104029299	104057236	2.51E-02	8.19E-01	4.40E-01	8.18E-01	positive regulation of mitochondrion organization
GO: 32389	5395	PMS2	7	6012870	6048737	2.58E-02	3.66E-01	8.84E-03	1.91E-05	MutLalpha complex
GO: 32300	5395	PMS2	7	6012870	6048737	2.58E-02	3.66E-01	8.84E-03	1.91E-05	mismatch repair complex
GO: 30983	5395	PMS2	7	6012870	6048737	2.58E-02	3.66E-01	8.84E-03	1.91E-05	mismatched DNA binding
KEGG 3430	5395	PMS2	7	6012870	6048737	2.58E-02	3.66E-01	8.84E-03	1.91E-05	KEGG_MISMATCH_REPAIR
GO: 6298	5395	PMS2	7	6012870	6048737	2.58E-02	3.66E-01	8.84E-03	1.91E-05	mismatch repair
GO: 32407	5395	PMS2	7	6012870	6048737	2.58E-02	3.66E-01	8.84E-03	1.91E-05	MutSalpha complex binding
GO: 30983	4439	MSH5	6	31707725	31730455	4.35E-02	8.54E-01	7.73E-01	5.14E-01	mismatched DNA binding
GO: 6298	4439	MSH5	6	31707725	31730455	4.35E-02	8.54E-01	7.73E-01	5.14E-01	mismatch repair
KEGG 3430	5982	RFC2	7	73645832	73668738	4.80E-02	5.91E-01	2.02E-02	4.46E-01	KEGG_MISMATCH_REPAIR
GO: 30983	7508	XPC	3	14186647	14220172	5.52E-02	1.04E-01	2.77E-02	5.53E-01	mismatched DNA binding
KEGG 3430	6119	RPA3	7	7676575	7758238	6.55E-02	7.22E-01	9.17E-02	4.40E-01	KEGG_MISMATCH_REPAIR
GO: 32300	4292	MLH1	3	37034841	37092337	6.98E-02	3.97E-04	1.28E-04	4.13E-04	mismatch repair complex
GO: 6298	4292	MLH1	3	37034841	37092337	6.98E-02	3.97E-04	1.28E-04	4.13E-04	mismatch repair
KEGG 3430	4292	MLH1	3	37034841	37092337	6.98E-02	3.97E-04	1.28E-04	4.13E-04	KEGG_MISMATCH_REPAIR
GO: 30983	4292	MLH1	3	37034841	37092337	6.98E-02	3.97E-04	1.28E-04	4.13E-04	mismatched DNA binding
GO: 32407	4292	MLH1	3	37034841	37092337	6.98E-02	3.97E-04	1.28E-04	4.13E-04	MutSalpha complex binding
GO: 32389	4292	MLH1	3	37034841	37092337	6.98E-02	3.97E-04	1.28E-04	4.13E-04	MutLalpha complex
GO: 33683	2067	ERCC1	19	45910591	45927177	7.32E-02	3.96E-01	2.69E-01	3.30E-01	nucleotide-excision repair, DNA incision
GO: 32407	545	ATR	3	142168077	142297668	7.62E-02	7.94E-01	2.71E-01	2.97E-01	MutSalpha complex binding
GO: 90140	79594	MUL1	1	20825941	20834674	8.94E-02	5.22E-01	5.27E-01	4.68E-01	regulation of mitochondrial fission
GO: 90141	79594	MUL1	1	20825941	20834674	8.94E-02	5.22E-01	5.27E-01	4.68E-01	positive regulation of mitochondrial fission
GO: 10822	79594	MUL1	1	20825941	20834674	8.94E-02	5.22E-01	5.27E-01	4.68E-01	positive regulation of mitochondrion organization
GO: 90200	26355	FAM162A	3	122103023	122128961	1.32E-01	7.57E-01	6.93E-01	8.40E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	26355	FAM162A	3	122103023	122128961	1.32E-01	7.57E-01	6.93E-01	8.40E-01	positive regulation of mitochondrion organization
GO:1900063	56947	MFF	2	228192228	228222549	1.52E-01	9.63E-01	5.92E-01	3.29E-01	regulation of peroxisome organization
GO: 10822	56947	MFF	2	228192228	228222549	1.52E-01	9.63E-01	5.92E-01	3.29E-01	positive regulation of mitochondrion organization
GO: 90200	56947	MFF	2	228192228	228222549	1.52E-01	9.63E-01	5.92E-01	3.29E-01	positive regulation of release of cytochrome c from mitochondria
GO: 32389	7486	WRN	8	30890778	31031277	1.66E-01	5.59E-01	6.60E-01	3.60E-01	MutLalpha complex
GO: 32300	7486	WRN	8	30890778	31031277	1.66E-01	5.59E-01	6.60E-01	3.60E-01	mismatch repair complex
GO: 10822	637	BID	22	18216906	18257431	1.77E-01	2.99E-02	7.33E-02	2.11E-01	positive regulation of mitochondrion organization
GO: 90200	637	BID	22	18216906	18257431	1.77E-01	2.99E-02	7.33E-02	2.11E-01	positive regulation of release of cytochrome c from mitochondria
GO: 90141	54708	MARCH_5	10	94050920	94113721	1.81E-01	8.26E-03	4.51E-01	5.33E-02	positive regulation of mitochondrial fission
GO: 10822	54708	MARCH_5	10	94050920	94113721	1.81E-01	8.26E-03	4.51E-01	5.33E-02	positive regulation of mitochondrion organization
GO: 90140	54708	MARCH_5	10	94050920	94113721	1.81E-01	8.26E-03	4.51E-01	5.33E-02	regulation of mitochondrial fission
KEGG 3430	29935	RPA4	23	96138907	96140466	1.81E-01	N/A	N/A	N/A	KEGG_MISMATCH_REPAIR
GO: 10822	572	BAD	11	64037300	64052176	1.87E-01	2.48E-01	4.16E-01	1.79E-01	positive regulation of mitochondrion organization
GO: 90200	572	BAD	11	64037300	64052176	1.87E-01	2.48E-01	4.16E-01	1.79E-01	positive regulation of release of cytochrome c from mitochondria
GO: 33683	2071	ERCC3	2	128014866	128051752	1.97E-01	4.27E-01	8.61E-01	7.39E-03	nucleotide-excision repair, DNA incision

GO: 10822	708	C1QBP	17	5336099	5342471	2.05E-01	8.72E-01	2.59E-01	5.99E-01	positive regulation of mitochondrion organization
GO:1900063	57506	MAVS	20	3827446	3856770	2.13E-01	7.14E-02	2.31E-01	8.82E-01	regulation of peroxisome organization
GO: 10822	5366	PMAIP1	18	57567192	57571538	2.38E-01	1.05E-01	2.58E-02	1.10E-01	positive regulation of mitochondrion organization
GO: 90200	5366	PMAIP1	18	57567192	57571538	2.38E-01	1.05E-01	2.58E-02	1.10E-01	positive regulation of release of cytochrome c from mitochondria
GO: 90200	29108	PYCARD	16	31212807	31214097	2.44E-01	4.42E-01	1.57E-01	N/A	positive regulation of release of cytochrome c from mitochondria
GO: 10822	29108	PYCARD	16	31212807	31214097	2.44E-01	4.42E-01	1.57E-01	N/A	positive regulation of mitochondrion organization
GO: 30983	2956	MSH6	2	48010221	48034092	2.46E-01	3.15E-01	1.58E-01	9.36E-02	mismatched DNA binding
GO: 32300	2956	MSH6	2	48010221	48034092	2.46E-01	3.15E-01	1.58E-01	9.36E-02	mismatch repair complex
KEGG 3430	2956	MSH6	2	48010221	48034092	2.46E-01	3.15E-01	1.58E-01	9.36E-02	KEGG_MISMATCH_REPAIR
GO: 6298	2956	MSH6	2	48010221	48034092	2.46E-01	3.15E-01	1.58E-01	9.36E-02	mismatch repair
GO: 10822	51100	SH3GLB1	1	87170253	87213867	2.55E-01	7.63E-01	2.92E-01	5.27E-01	positive regulation of mitochondrion organization
GO: 90141	664	BNIP3	10	133781204	133795435	2.63E-01	1.17E-01	7.70E-01	7.19E-01	positive regulation of mitochondrial fission
GO: 90140	664	BNIP3	10	133781204	133795435	2.63E-01	1.17E-01	7.70E-01	7.19E-01	regulation of mitochondrial fission
GO: 10822	664	BNIP3	10	133781204	133795435	2.63E-01	1.17E-01	7.70E-01	7.19E-01	positive regulation of mitochondrion organization
GO: 90200	664	BNIP3	10	133781204	133795435	2.63E-01	1.17E-01	7.70E-01	7.19E-01	positive regulation of release of cytochrome c from mitochondria
GO: 32407	4595	MUTYH	1	45794914	45806142	2.75E-01	4.31E-01	1.97E-01	1.97E-01	MutSalpha complex binding
GO: 6298	4595	MUTYH	1	45794914	45806142	2.75E-01	4.31E-01	1.97E-01	1.97E-01	mismatch repair
GO: 10822	2810	SFN	1	27189633	27190947	2.78E-01	4.30E-01	2.23E-01	7.65E-01	positive regulation of mitochondrion organization
KEGG 3430	5424	POLD1	19	50887580	50921275	2.84E-01	6.48E-01	6.86E-01	2.11E-01	KEGG_MISMATCH_REPAIR
KEGG 3430	6118	RPA2	1	28218049	28241236	2.94E-01	2.04E-02	1.18E-01	7.45E-01	KEGG_MISMATCH_REPAIR
GO: 6298	2072	ERCC4	16	14014014	14046205	3.00E-01	5.58E-01	2.66E-01	6.21E-01	mismatch repair
GO: 33683	2072	ERCC4	16	14014014	14046205	3.00E-01	5.58E-01	2.66E-01	6.21E-01	nucleotide-excision repair, DNA incision
KEGG 3430	5983	RFC3	13	34392206	34540695	3.15E-01	7.80E-01	7.18E-01	6.12E-01	KEGG_MISMATCH_REPAIR
GO: 90200	7157	TP53	17	7571720	7590868	3.21E-01	5.79E-01	2.20E-01	2.47E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	7157	TP53	17	7571720	7590868	3.21E-01	5.79E-01	2.20E-01	2.47E-01	positive regulation of mitochondrion organization
GO: 10822	207	AKT1	14	105235686	105262080	3.62E-01	4.10E-01	5.64E-01	3.96E-01	positive regulation of mitochondrion organization
KEGG 3430	5981	RFC1	4	39289069	39368001	3.64E-01	6.29E-01	7.60E-01	6.19E-01	KEGG_MISMATCH_REPAIR
GO: 90200	581	BAX	19	49458117	49465055	3.65E-01	1.25E-01	2.47E-01	8.13E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	581	BAX	19	49458117	49465055	3.65E-01	1.25E-01	2.47E-01	8.13E-01	positive regulation of mitochondrion organization
GO: 90200	90427	BMF	15	40380091	40401075	3.71E-01	5.25E-02	3.21E-02	5.08E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	90427	BMF	15	40380091	40401075	3.71E-01	5.25E-02	3.21E-02	5.08E-01	positive regulation of mitochondrion organization
GO: 10822	10891	PPARGC1A	4	23793644	23891700	3.79E-01	1.49E-01	1.47E-01	3.43E-01	positive regulation of mitochondrion organization
GO: 10822	65018	PINK1	1	20959948	20978004	3.83E-01	8.71E-01	5.33E-01	4.83E-01	positive regulation of mitochondrion organization
GO: 90200	65018	PINK1	1	20959948	20978004	3.83E-01	8.71E-01	5.33E-01	4.83E-01	positive regulation of release of cytochrome c from mitochondria
GO: 90200	10962	MLLT11	1	151032151	151040973	3.90E-01	7.62E-01	9.23E-01	4.75E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	10962	MLLT11	1	151032151	151040973	3.90E-01	7.62E-01	9.23E-01	4.75E-01	positive regulation of mitochondrion organization
GO: 32300	4436	MSH2	2	47630206	47710367	3.98E-01	3.10E-01	7.03E-01	5.49E-01	mismatch repair complex
GO: 30983	4436	MSH2	2	47630206	47710367	3.98E-01	3.10E-01	7.03E-01	5.49E-01	mismatched DNA binding
GO: 6298	4436	MSH2	2	47630206	47710367	3.98E-01	3.10E-01	7.03E-01	5.49E-01	mismatch repair

KEGG 3430	4436	MSH2	2	47630206	47710367	3.98E-01	3.10E-01	7.03E-01	5.49E-01	KEGG_MISMATCH_REPAIR
GO: 10822	841	CASP8	2	202098166	202152434	4.15E-01	8.81E-01	4.49E-01	3.35E-01	positive regulation of mitochondrion organization
GO: 10822	7533	YWHAH	22	32340479	32353590	4.25E-01	7.16E-01	2.86E-01	6.25E-01	positive regulation of mitochondrion organization
GO: 10822	8655	DYNLL1	12	120907660	120936298	4.50E-01	3.11E-01	4.07E-01	4.21E-01	positive regulation of mitochondrion organization
GO: 32407	5378	PMS1	2	190648811	190742355	4.57E-01	8.23E-01	3.36E-01	7.24E-02	MutSalpha complex binding
GO: 32389	5378	PMS1	2	190648811	190742355	4.57E-01	8.23E-01	3.36E-01	7.24E-02	MutLalpha complex
GO: 32300	5378	PMS1	2	190648811	190742355	4.57E-01	8.23E-01	3.36E-01	7.24E-02	mismatch repair complex
GO: 30983	5378	PMS1	2	190648811	190742355	4.57E-01	8.23E-01	3.36E-01	7.24E-02	mismatched DNA binding
GO: 6298	5378	PMS1	2	190648811	190742355	4.57E-01	8.23E-01	3.36E-01	7.24E-02	mismatch repair
GO: 33683	2073	ERCC5	13	103498191	103528351	4.73E-01	7.10E-01	3.43E-01	2.62E-01	nucleotide-excision repair, DNA incision
GO: 10822	7755	ZNF205	16	3162563	3170518	4.74E-01	9.01E-01	7.24E-01	9.47E-01	positive regulation of mitochondrion organization
GO:90200	8743	TNFSF10	3	172223298	172241297	4.77E-01	6.95E-01	6.77E-01	6.09E-01	positive regulation of release of cytochrome c from mitochondria
GO:10822	8743	TNFSF10	3	172223298	172241297	4.77E-01	6.95E-01	6.77E-01	6.09E-01	positive regulation of mitochondrion organization
KEGG 3430	6742	SSBP1	7	141438121	141450288	4.81E-01	8.18E-01	8.67E-01	5.17E-01	KEGG_MISMATCH_REPAIR
GO:10822	28958	COA3	17	40949652	40950704	4.87E-01	1.75E-03	5.11E-01	N/A	positive regulation of mitochondrion organization
GO:6298	11277	TREX1	3	48506919	48509044	4.91E-01	4.76E-01	7.94E-01	4.11E-01	mismatch repair
GO:32407	11277	TREX1	3	48506919	48509044	4.91E-01	4.76E-01	7.94E-01	4.11E-01	MutSalpha complex binding
GO:33683	22909	FAN1	15	31196055	31235311	5.30E-01	2.16E-06	1.15E-04	2.10E-09	nucleotide-excision repair, DNA incision
GO:10822	10572	SIVA1	14	105219470	105225996	5.32E-01	1.48E-01	6.74E-01	8.89E-01	positive regulation of mitochondrion organization
GO:6298	9156	EXO1	1	242011493	242053241	5.56E-01	9.35E-01	9.03E-01	2.23E-01	mismatch repair
KEGG 3430	9156	EXO1	1	242011493	242053241	5.56E-01	9.35E-01	9.03E-01	2.23E-01	KEGG_MISMATCH_REPAIR
GO: 90200	10105	PPIF	10	81107220	81115090	5.62E-01	2.02E-01	4.28E-01	4.88E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	10105	PPIF	10	81107220	81115090	5.62E-01	2.02E-01	4.28E-01	4.88E-01	positive regulation of mitochondrion organization
GO: 6298	7161	TP73	1	3569129	3652765	5.69E-01	3.18E-01	4.40E-01	5.54E-01	mismatch repair
GO:10822	7531	YWHAE	17	1247834	1303556	5.70E-01	8.16E-01	4.96E-01	5.15E-01	positive regulation of mitochondrion organization
GO: 10822	7532	YWHAG	7	75956108	75988342	5.78E-01	4.82E-01	9.74E-01	8.36E-02	positive regulation of mitochondrion organization
GO: 10822	7534	YWHAZ	8	101930804	101965623	5.89E-01	1.51E-01	1.89E-01	5.93E-02	positive regulation of mitochondrion organization
GO: 90140	64423	INF2	14	105155943	105185947	5.93E-01	2.11E-01	2.83E-01	5.52E-01	regulation of mitochondrial fission
GO: 10822	578	BAK1	6	33540323	33548070	5.98E-01	7.98E-01	7.78E-01	3.03E-01	positive regulation of mitochondrion organization
GO: 90200	578	BAK1	6	33540323	33548070	5.98E-01	7.98E-01	7.78E-01	3.03E-01	positive regulation of release of cytochrome c from mitochondria
GO: 33683	4913	NTHL1	16	2089816	2097867	6.25E-01	5.50E-01	4.66E-01	6.35E-01	nucleotide-excision repair, DNA incision
GO: 90200	10018	BCL2L11	2	111878491	111926022	6.27E-01	8.58E-01	8.05E-01	1.51E-02	positive regulation of release of cytochrome c from mitochondria
GO: 10822	10018	BCL2L11	2	111878491	111926022	6.27E-01	8.58E-01	8.05E-01	1.51E-02	positive regulation of mitochondrion organization
GO: 10822	4836	NMT1	17	43138680	43186384	6.37E-01	9.42E-01	9.35E-01	4.65E-01	positive regulation of mitochondrion organization
GO: 10822	10971	YWHAQ	2	9724106	9771106	6.38E-01	1.92E-01	6.28E-01	7.69E-01	positive regulation of mitochondrion organization
GO: 10822	7529	YWHAB	20	43514344	43537161	6.50E-01	2.53E-01	4.98E-01	8.31E-01	positive regulation of mitochondrion organization
GO: 6298	10714	POLD3	11	74303575	74354105	6.51E-01	8.79E-01	6.36E-01	1.52E-01	mismatch repair
KEGG 3430	10714	POLD3	11	74303575	74354105	6.51E-01	8.79E-01	6.36E-01	1.52E-01	KEGG_MISMATCH_REPAIR
GO: 30983	6996	TDG	12	104359593	104382656	6.84E-01	1.83E-01	2.10E-01	4.78E-01	mismatched DNA binding

GO: 6298	6996	TDG	12	104359593	104382656	6.84E-01	1.83E-01	2.10E-01	4.78E-01	mismatch repair
GO: 90140	1723	DHODH	16	72042643	72059316	6.96E-01	9.59E-01	7.30E-01	4.85E-01	regulation of mitochondrial fission
GO: 6298	25	ABL1	9	133589268	133763062	6.97E-01	6.47E-01	9.21E-01	1.81E-01	mismatch repair
GO: 30983	4438	MSH4	1	76262556	76378923	7.24E-01	2.05E-01	2.13E-01	1.40E-01	mismatched DNA binding
KEGG 3430	5985	RFC5	12	118454506	118470044	7.38E-01	1.15E-01	2.33E-01	3.95E-01	KEGG_MISMATCH_REPAIR
GO:190006 3	1005 9	DNM1L	12	32832137	32898584	7.55E-01	8.32E-01	6.94E-01	1.36E-03	regulation of peroxisome organization
GO: 90141	1005 9	DNM1L	12	32832137	32898584	7.55E-01	8.32E-01	6.94E-01	1.36E-03	positive regulation of mitochondrial fission
GO: 90200	1005 9	DNM1L	12	32832137	32898584	7.55E-01	8.32E-01	6.94E-01	1.36E-03	positive regulation of release of cytochrome c from mitochondria
GO: 10822	1005 9	DNM1L	12	32832137	32898584	7.55E-01	8.32E-01	6.94E-01	1.36E-03	positive regulation of mitochondrion organization
GO: 90140	1005 9	DNM1L	12	32832137	32898584	7.55E-01	8.32E-01	6.94E-01	1.36E-03	regulation of mitochondrial fission
KEGG 3430	6117	RPA1	17	1733273	1802848	7.75E-01	2.96E-01	5.51E-01	4.76E-01	KEGG_MISMATCH_REPAIR
GO: 10822	5533	PPP3CC	8	22298483	22398657	7.99E-01	4.58E-01	7.29E-01	3.38E-01	positive regulation of mitochondrion organization
KEGG 3430	5984	RFC4	3	186507681	186524484	8.08E-01	7.04E-01	7.95E-01	3.01E-01	KEGG_MISMATCH_REPAIR
GO: 4748	6240	RRM1	11	4115924	4160106	8.20E-01	6.60E-01	9.85E-01	3.40E-01	ribonucleoside-diphosphate reductase activity, thioredoxin disulfide as acceptor
GO: 16728	6240	RRM1	11	4115924	4160106	8.20E-01	6.60E-01	9.85E-01	3.40E-01	oxidoreductase activity, acting on CH or CH2 groups, disulfide as acceptor
GO: 30983	5111	PCNA	20	5095599	5107268	8.29E-01	2.76E-01	6.40E-01	3.55E-01	mismatched DNA binding
KEGG 3430	5111	PCNA	20	5095599	5107268	8.29E-01	2.76E-01	6.40E-01	3.55E-01	KEGG_MISMATCH_REPAIR
GO: 6298	5111	PCNA	20	5095599	5107268	8.29E-01	2.76E-01	6.40E-01	3.55E-01	mismatch repair
GO: 90200	638	BIK	22	43506754	43525718	8.52E-01	6.42E-01	8.52E-01	1.19E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	638	BIK	22	43506754	43525718	8.52E-01	6.42E-01	8.52E-01	1.19E-01	positive regulation of mitochondrion organization
GO: 10822	596	BCL2	18	60790579	60986613	8.65E-01	5.93E-01	4.81E-01	6.54E-01	positive regulation of mitochondrion organization
GO: 10822	3002	GZMB	14	25100160	25103432	8.84E-01	8.26E-01	8.18E-01	6.33E-01	positive regulation of mitochondrion organization
GO: 10822	2711 3	BBC3	19	47724079	47736023	8.89E-01	4.98E-01	7.87E-01	2.78E-01	positive regulation of mitochondrion organization
GO: 90200	2711 3	BBC3	19	47724079	47736023	8.89E-01	4.98E-01	7.87E-01	2.78E-01	positive regulation of release of cytochrome c from mitochondria
GO: 16728	6241	RRM2	2	10262695	10271546	8.96E-01	3.35E-01	3.69E-01	2.65E-01	oxidoreductase activity, acting on CH or CH2 groups, disulfide as acceptor
GO: 4748	6241	RRM2	2	10262695	10271546	8.96E-01	3.35E-01	3.69E-01	2.65E-01	ribonucleoside-diphosphate reductase activity, thioredoxin disulfide as acceptor
GO: 10822	8398	PLA2G6	22	38507502	38577836	9.01E-01	2.91E-01	6.64E-01	1.80E-01	positive regulation of mitochondrion organization
GO: 90200	8398	PLA2G6	22	38507502	38577836	9.01E-01	2.91E-01	6.64E-01	1.80E-01	positive regulation of release of cytochrome c from mitochondria
GO: 90200	8739	HRK	12	117299027	117319232	9.10E-01	6.48E-01	8.21E-01	4.30E-01	positive regulation of release of cytochrome c from mitochondria
GO: 10822	8739	HRK	12	117299027	117319232	9.10E-01	6.48E-01	8.21E-01	4.30E-01	positive regulation of mitochondrion organization
GO: 10822	5599	MAPK8	10	49609687	49643183	9.32E-01	7.42E-01	8.49E-01	7.87E-01	positive regulation of mitochondrion organization
GO: 4748	5048 4	RRM2B	8	103216729	103251346	9.38E-01	6.29E-01	8.45E-01	6.44E-06	ribonucleoside-diphosphate reductase activity, thioredoxin disulfide as acceptor
GO: 16728	5048 4	RRM2B	8	103216729	103251346	9.38E-01	6.29E-01	8.45E-01	6.44E-06	oxidoreductase activity, acting on CH or CH2 groups, disulfide as acceptor
GO: 10822	1407 35	DYNLL2	17	56160780	56167618	9.58E-01	8.08E-01	8.19E-01	8.93E-01	positive regulation of mitochondrion organization
KEGG 3430	5780 4	POLD4	11	67118236	67121067	9.59E-01	6.48E-01	9.21E-01	3.74E-01	KEGG_MISMATCH_REPAIR
GO: 10822	8470 9	MGARP	4	140187317	140201492	9.78E-01	8.81E-01	8.98E-01	1.51E-01	positive regulation of mitochondrion organization

Supplementary Table 13: Setscreen enrichment p-values for the Pearl et al. (2015) pathways in TRACK-HD, REGISTRY, the TRACK-HD meta-analysis and GeM

Gene Set	p(TRACK)	p(REGISTRY)	p(META)	p (GeM)	Description1	Description2	Description3	Description4
2071015	9.05E-07	4.43E-03	2.93E-11	2.01E-02	Repair_pathway	SSR	MMR	Mismatch_and_loop_recognition_factors
2071000	2.43E-06	6.85E-02	1.49E-14	5.15E-04	Repair_pathway	SSR	MMR	
2070000	5.77E-03	4.76E-02	3.32E-07	1.42E-02	Repair_pathway	SSR		
2071017	1.95E-02	2.44E-02	5.84E-05	8.92E-08	Repair_pathway	SSR	MMR	MutL_homologs
2111513	4.71E-02	2.55E-01	8.12E-01	2.86E-03	Repair_pathway	Associated_process	TLS	DNA_polymerases
2070600	5.02E-02	7.99E-01	1.10E-01	2.92E-01	Repair_pathway	SSR	NER	
2070607	5.18E-02	7.61E-01	3.02E-02	2.26E-01	Repair_pathway	SSR	NER	TCR_(Transcription_coupled_repair)
2071104	5.35E-02	3.90E-01	2.07E-02	5.37E-02	Repair_pathway	SSR	BER	LONG_PATCH-BER_factors
2022100	6.69E-02	3.19E-02	7.21E-04	7.29E-02	Repair_pathway	DSR	Alt-NHEJ	
1100000	7.52E-02	6.14E-01	1.94E-01	6.13E-01	Associated_process	DNA_replication		
1080700	8.99E-02	8.35E-01	2.82E-01	4.92E-01	Associated_process	Checkpoint_factors	S-CC_phase	
1051930	1.02E-01	5.68E-01	1.30E-01	7.62E-01	Associated_process	Ubiquitin_response	Ubiquitin-_conjugating_enzymes_(E2)	UBL-conjugating_enzymes
2000000	1.13E-01	2.60E-01	1.03E-03	1.11E-02	Repair_pathway			
2070605	1.14E-01	5.00E-01	8.14E-01	4.64E-01	Repair_pathway	SSR	NER	DNA_polymerase_epsilon
1030000	1.59E-01	1.90E-01	3.59E-01	2.63E-01	Associated_process	Telomere_maintenance		
2070606	1.60E-01	9.56E-01	6.55E-01	5.49E-01	Repair_pathway	SSR	NER	DNA_polymerase_kappa
2071020	1.73E-01	3.14E-01	9.86E-03	7.97E-02	Repair_pathway	SSR	MMR	Other_MMR_factors
1051900	1.97E-01	7.69E-01	1.71E-01	8.19E-01	Associated_process	Ubiquitin_response	Ubiquitin-_conjugating_enzymes_(E2)	
2071023	2.15E-01	1.73E-01	7.67E-02	5.90E-01	Repair_pathway	SSR	MMR	RPA_(replication_factor_A)
1081300	2.15E-01	8.71E-01	4.25E-01	6.96E-01	Associated_process	Checkpoint_factors	HRAD17(Rad24)-_RFC_complex	
1051208	2.41E-01	2.50E-01	3.12E-01	5.81E-01	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	single_Ring-finger_type_E3
1080900	2.50E-01	4.77E-01	9.41E-01	2.74E-01	Associated_process	Checkpoint_factors	G1-S_checkpoint	
2071003	2.58E-01	8.68E-01	3.40E-01	1.57E-01	Repair_pathway	SSR	MMR	DNA_polymerase_delta
1051222	2.87E-01	2.82E-01	1.50E-01	6.61E-01	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	Riddle_syndrome!
1080800	2.87E-01	3.88E-01	7.69E-01	2.52E-01	Associated_process	Checkpoint_factors	G1-CC_phase	
2070603	2.92E-01	8.34E-01	5.37E-01	4.50E-01	Repair_pathway	SSR	NER	DNA_polymerase_delta
2071010	2.92E-01	7.60E-01	6.37E-01	7.12E-01	Repair_pathway	SSR	MMR	RFC_(replication_factor_C)
1051221	3.18E-01	1.56E-01	1.06E-02	2.79E-01	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	Other_single_Ring-_finger_type_E3
1010000	3.23E-01	4.39E-01	3.23E-01	8.30E-01	Associated_process	Chromatin_remodelling		
1051829	3.28E-01	5.91E-01	5.58E-01	9.17E-01	Associated_process	Ubiquitin_response	Ubiquitin-_activating_enzymes_(E1)	UBL-activating_enzymes
1051800	3.29E-01	5.91E-01	5.58E-01	9.17E-01	Associated_process	Ubiquitin_response	Ubiquitin-_activating_enzymes_(E1)	
1051927	3.31E-01	7.89E-01	4.15E-01	6.74E-01	Associated_process	Ubiquitin_response	Ubiquitin-_conjugating_enzymes_(E2)	Ubiquitin-conjugating_enzymes
3060000	3.41E-01	1.70E-01	3.61E-01	7.39E-01	Genes_with_probable_DDR_role	Direct_Repair_(not_in_humans)		

1031600	3.86E-01	8.44E-01	5.12E-01	6.69E-01	Associated_process	Telomere_maintenance	Alternative_mechanism	
1031616	3.86E-01	8.44E-01	5.12E-01	6.69E-01	Associated_process	Telomere_maintenance	Alternative_mechanism	MRN_Complex
2020200	4.09E-01	6.98E-01	5.00E-01	4.77E-01	Repair_pathway	DSR	HR_(Homologous_Recombination)	
1052000	4.20E-01	3.11E-01	4.35E-01	8.24E-01	Associated_process	Ubiquitin_response	Ubiquitins_and_Ubiquitin-like_proteins	
1052028	4.20E-01	3.11E-01	4.35E-01	8.24E-01	Associated_process	Ubiquitin_response	Ubiquitins_and_Ubiquitin-like_proteins	Ubiquitins
1000000	4.26E-01	4.38E-01	5.76E-01	3.21E-01	Associated_process			
1082500	4.29E-01	1.79E-01	5.65E-01	6.91E-01	Associated_process	Checkpoint_factors	FPC_(fork_protection_complex)	
2111531	4.30E-01	2.91E-01	2.99E-01	7.84E-01	Repair_pathway	Associated_process	TLS	Y-family_DNA_polymerases
2071018	4.44E-01	2.64E-01	2.34E-01	1.12E-01	Repair_pathway	SSR	MMR	MutS_homologs_specialized_for_meiosis
2110000	4.48E-01	4.49E-01	5.96E-01	4.80E-02	Repair_pathway	Associated_process		
2111500	4.48E-01	4.49E-01	5.96E-01	4.80E-02	Repair_pathway	Associated_process	TLS	
2020000	4.71E-01	4.39E-01	8.35E-02	4.20E-02	Repair_pathway	DSR		
1050500	4.76E-01	8.55E-01	8.56E-01	7.18E-01	Associated_process	Ubiquitin_response	Deubiquitinating_enzyme_(DUB)	
1050501	4.76E-01	8.55E-01	8.56E-01	7.18E-01	Associated_process	Ubiquitin_response	Deubiquitinating_enzyme_(DUB)	UBL-specific_proteases_(ULPs)
1080000	4.86E-01	4.50E-01	8.20E-01	2.85E-01	Associated_process	Checkpoint_factors		
2072800	4.97E-01	5.82E-01	7.02E-02	3.98E-02	Repair_pathway	SSR	Other_SSR_genes	
2020400	5.07E-01	7.84E-01	8.18E-01	5.80E-01	Repair_pathway	DSR	NHEJ	
2071100	5.18E-01	1.14E-01	2.76E-01	1.65E-01	Repair_pathway	SSR	BER	
1082600	5.20E-01	5.64E-01	6.17E-01	5.95E-01	Associated_process	Checkpoint_factors	G2-CC_phase	
1090000	5.70E-01	5.67E-01	6.15E-01	6.62E-01	Associated_process	p53_pathway		
1050000	5.88E-01	3.44E-01	2.17E-01	7.47E-01	Associated_process	Ubiquitin_response		
2070602	5.93E-01	1.61E-01	3.08E-01	5.35E-01	Repair_pathway	SSR	NER	GGR_(Global_genome_repair)
2020300	6.05E-01	5.24E-01	6.24E-01	8.22E-01	Repair_pathway	DSR	Other_DSR_genes	
2071119	6.09E-01	6.72E-02	9.07E-01	2.64E-01	Repair_pathway	SSR	BER	Other_BER_factors
2071111	6.11E-01	2.27E-01	5.24E-01	9.70E-01	Repair_pathway	SSR	BER	AP_endonucleases
1082700	6.14E-01	6.85E-01	9.25E-01	1.51E-01	Associated_process	Checkpoint_factors	G2-M_checkpoint	
2021400	6.22E-01	4.96E-02	1.45E-01	9.20E-01	Repair_pathway	DSR	HR_(Homologous Recombination)	
1051700	6.42E-01	4.61E-01	5.63E-01	1.52E-01	Associated_process	Ubiquitin_response	Ubiquitin-like_proteins_(UBLs)	
1051725	6.42E-01	4.61E-01	5.63E-01	1.52E-01	Associated_process	Ubiquitin_response	Ubiquitin-like_proteins_(UBLs)	SUMO
1051200	6.61E-01	7.44E-02	5.58E-02	3.70E-01	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	
1082900	6.63E-01	8.72E-01	8.87E-01	4.58E-01	Associated_process	Checkpoint_factors	Rad17-Mec3-_Ddc1_complex	
1082200	6.69E-01	8.04E-02	2.30E-01	2.61E-01	Associated_process	Checkpoint_factors	damage_in_S_phase	
2111514	7.20E-01	5.25E-01	7.10E-01	4.37E-01	Repair_pathway	Associated_process	TLS	epistasis_group

2020100	7.23E-01	5.41E-01	5.70E-01	2.93E-04	Repair_pathway	DSR	FA_(Fanconi_anemia_pathway)	
1040000	7.46E-01	5.93E-01	6.62E-01	3.78E-01	Associated_process	Chromosome_segregation		
3000000	7.86E-01	6.19E-01	3.00E-01	7.39E-01	Genes_with_probable_DDR_role			
2072300	7.97E-01	3.24E-01	8.88E-01	8.75E-01	Repair_pathway	SSR	Direct_Repair	
2072400	8.27E-01	3.89E-03	6.87E-02	2.76E-01	Repair_pathway	SSR	DNA_replication	
2071124	8.39E-01	8.94E-01	8.19E-01	3.16E-01	Repair_pathway	SSR	BER	SHORT_PATCH-BER_factors
2071112	9.02E-01	1.67E-01	3.58E-01	5.51E-01	Repair_pathway	SSR	BER	DNA_glycosylases
1051209	9.25E-01	1.38E-02	5.59E-02	7.56E-01	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	single_Ring-finger_type_E4
1120000	9.58E-01	6.23E-01	9.97E-01	6.78E-05	Associated_process	Modulation_of_nucleotide_pools		
1083000	9.62E-01	7.83E-01	9.16E-01	8.57E-01	Associated_process	Checkpoint_factors	RAD9-Hus1-Rad1_complex	

Supplementary Table 14: Gene-wide p-values for the most significant genes in the two Pearl et al. pathways showing significant enrichment in TRACK

Entrez	Gene Symbol	Chr	Start	End	p(TRACK)	p(REG)	p(META)	p(GeM)	Pathways
4437	MSH3	5	79950467	80172634	2.94E-08	9.52E-04	8.88E-11	1.98E-02	Repair_pathway/SSR/MMR/Mismatch_and_loop_recognition_factors
5425	POLD2	7	44154279	44163169	7.21E-04	3.12E-01	2.75E-03	5.17E-01	Repair_pathway/SSR/MMR
3978	LIG1	19	48618703	48673560	1.65E-02	8.28E-02	5.35E-04	6.39E-02	Repair_pathway/SSR/MMR
27030	MLH3	14	75480467	75518235	1.69E-02	6.69E-01	1.47E-01	6.39E-03	Repair_pathway/SSR/MMR
5395	PMS2	7	6012870	6048737	2.58E-02	3.66E-01	8.84E-03	1.76E-05	Repair_pathway/SSR/MMR
4439	MSH5	6	31707725	31730455	4.35E-02	8.54E-01	7.73E-01	5.11E-01	Repair_pathway/SSR/MMR
5982	RFC2	7	73645832	73668738	4.80E-02	5.91E-01	2.02E-02	4.44E-01	Repair_pathway/SSR/MMR
6119	RPA3	7	7676575	7758238	6.55E-02	7.22E-01	9.17E-02	4.37E-01	Repair_pathway/SSR/MMR
4292	MLH1	3	37034841	37092337	6.98E-02	3.97E-04	1.28E-04	3.91E-04	Repair_pathway/SSR/MMR

Supplementary Table 15: Summary of missing data in REGISTRY

Variable	N	Missing Values	
		Count	Percent
Motor	1744	91	4.96
Verbal Fluency	1145	690	37.6
Stroop Color	1052	783	42.67
Stroop Color	1116	719	39.18
Stroop Word	1104	731	39.84
Stroop Interference	1092	743	40.49
TFC	1758	77	4.2
FAS score	1616	219	11.93

Supplementary Table 16: Parameter estimates of variables in the model used to generate the REGISTRY cross sectional severity score. Multiple imputation adjusted estimates of statistical significance are given. CPO_1: clinical probability of onset; CPO_2: single transformation of clinical probability of onset. DF: degrees of freedom.

Parameter Estimates								
Parameter	**gender**	**Estimate**	**Std Error**	**95% Confidence Limits**		**DF**	**t for H0:**	**P Val**
Intercept		2.075589	0.267283	1.55102	2.60016	897.01	7.77	<.0001
cpo_1		-0.9142	0.21009	-1.32638	-0.50201	1191.6	-4.35	<.0001
cpo_2		-7.00283	0.911001	-8.79025	-5.2154	1141.5	-7.69	<.0001
cag		-0.01919	0.005133	-0.02927	-0.00912	862.96	-3.74	0.0002
gender	F	-0.13631	0.042605	-0.21992	-0.05271	1030.1	-3.2	0.0014
gender	M	0	0	.	.	.	.	.

Supplementary Table 17: Proportion of variance among variables present in TRACK-HD and REGISTRY which are accounted for by the first PC in the combined analysis.

Factor Pattern	
	Factor1
sqrtMotRaw	-0.91567
SDMT_correct	0.90797
SWR_correct	0.87904
tfc	0.86045

Supplementary Table 18: Effect of removing MSH3 on the Setscreen enrichment p-values for the top 14 GeM pathways in TRACK-HD, REGISTRY and the TRACK-REGISTRY meta-analysis.

Pathway	p(TRACK)	p(TRACKnoMSH3)	p(REGISTRY)	p(REGISTRYnoMSH3)	p(META)	p(METAnoMSH3)	Description
GO:32300	3.455E-09	0.04127	0.0008336	0.07162	1.13E-11	0.001024	mismatch repair complex
KEGG 3430	2.794E-07	0.04521	0.04795	0.1471	1.34E-16	0.000107	KEGG_MISMATCH_REPAIR
GO:30983	6.661E-07	0.1001	0.0004195	0.009264	3.17E-11	0.000274	mismatched DNA binding
GO:6298	0.000003533	0.2446	0.04589	0.1839	6.54E-09	0.0729	mismatch repair
GO:32407	0.01818	0.01818	0.1101	0.1101	0.000640	0.000640	MutSalpha complex binding
GO:32389	0.02249	0.02249	0.04688	0.04688	0.000523	0.000523	MutLalpha complex
GO:33683	0.08014	0.08014	0.0005874	0.0005874	0.00675	0.00675	nucleotide-excision repair, DNA incision
GO:90141	0.3318	0.3318	0.05934	0.05934	0.7872	0.7872	positive regulation of mitochondrial fission
GO:1900063	0.4103	0.4103	0.7287	0.7287	0.6926	0.6926	regulation of peroxisome organization
GO:90200	0.4582	0.4582	0.544	0.544	0.5280	0.5280	positive regulation of release of cytochrome c from mitochondria
GO:90140	0.5385	0.5385	0.3316	0.3316	0.8098	0.8098	regulation of mitochondrial fission
GO:10822	0.621	0.6228	0.6276	0.6276	0.8527	0.8527	positive regulation of mitochondrion organization
GO:4748	0.9639	0.9639	0.6974	0.6974	0.9792	0.9792	ribonucleoside-diphosphate reductase activity, thioredoxin disulfide as acceptor
GO:16728	0.9639	0.9639	0.6974	0.6974	0.9792	0.9792	oxidoreductase activity, acting on CH or CH2 groups, disulfide as acceptor

Supplementary Table 19: Effect of removing MSH3 on the Setscreen enrichment p-values for the Pearl et al. (2015) pathways in TRACK-HD, REGISTRY and the TRACK-REGISTRY meta-analysis.

Gene Set	p(TRACK)	p(TRACKnoMSH3)	p(REGISTRY)	p(REGISTRYnoMSH3)	p(META)	p(METAnoMSH3)	Description1	Description2	Description3	Description4
2071015	9.051E-07	0.3308	0.00443	0.2821	2.93E-11	0.5436	Repair_pathway	SSR	MMR	Mismatch_and_loop_recognition_factors
2071000	0.00000243	0.08225	0.06854	0.2285	1.49E-14	0.000127	Repair_pathway	SSR	MMR	
2070000	0.005767	0.2506	0.04762	0.1713	3.32E-07	0.0549	Repair_pathway	SSR		
2071017	0.01947	0.01947	0.02442	0.02442	5.84E-05	5.84E-05	Repair_pathway	SSR	MMR	MutL_homologs
2111513	0.04707	0.04707	0.2549	0.2549	0.8123	0.8123	Repair_pathway	Associated_process	TLS	DNA_polymerases
2070600	0.05024	0.05024	0.7989	0.7989	0.1098	0.1098	Repair_pathway	SSR	NER	

2070607	0.05177	0.05177	0.7606	0.7606	0.0302	0.0302	Repair_pathway	SSR	NER	TCR_(Transcription_coupled_repair)
2071104	0.05345	0.05345	0.3895	0.3895	0.0207	0.0207	Repair_pathway	SSR	BER	LONG_PATCH-BER_factors
2022100	0.0669	0.0669	0.03188	0.03188	0.00072	0.00072	Repair_pathway	DSR	Alt-NHEJ	
1100000	0.07519	0.07519	0.6138	0.6138	0.1939	0.1939	Associated_process	DNA_replication		
1080700	0.08987	0.08987	0.8346	0.8346	0.2817	0.2817	Associated_process	Checkpoint_factors	S-CC_phase	
1051930	0.1015	0.1015	0.5677	0.5677	0.1303	0.1303	Associated_process	Ubiquitin_response	Ubiquitin-_conjugating_enzymes_(E2)	UBL-conjugating_enzymes
2000000	0.1126	0.4184	0.2602	0.3906	0.0010	0.2586	Repair_pathway			
2070605	0.1144	0.1144	0.4998	0.4998	0.8140	0.8140	Repair_pathway	SSR	NER	DNA_polymerase_epsilon
1030000	0.1588	0.1588	0.1897	0.1897	0.3588	0.3588	Associated_process	Telomere_maintenance		
2070606	0.1596	0.1596	0.9556	0.9556	0.6550	0.6550	Repair_pathway	SSR	NER	DNA_polymerase_kappa
2071020	0.1726	0.1726	0.3142	0.3142	0.0099	0.0099	Repair_pathway	SSR	MMR	Other_MMR_factors
1051900	0.1973	0.1973	0.7689	0.7689	0.1711	0.1711	Associated_process	Ubiquitin_response	Ubiquitin-_conjugating_enzymes_(E2)	
2071023	0.2149	0.2149	0.1725	0.1725	0.0767	0.0767	Repair_pathway	SSR	MMR	RPA_(replication_factor_A)
1081300	0.215	0.215	0.8705	0.8705	0.4249	0.4249	Associated_process	Checkpoint_factors	HRAD17(Rad24)-_RFC_complex	
1051208	0.2409	0.2409	0.25	0.25	0.3120	0.3120	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	single_Ring-finger_type_E3
1080900	0.2499	0.2499	0.4774	0.4774	0.9412	0.9412	Associated_process	Checkpoint_factors	G1-S_checkpoint	
2071003	0.258	0.258	0.8678	0.8678	0.3397	0.3397	Repair_pathway	SSR	MMR	DNA_polymerase_delta
1051222	0.2873	0.2873	0.2823	0.2823	0.1495	0.1495	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	Riddle_syndrome!
1080800	0.2874	0.2874	0.3878	0.3878	0.7688	0.7688	Associated_process	Checkpoint_factors	G1-CC_phase	
2070603	0.292	0.292	0.8344	0.8344	0.5370	0.5370	Repair_pathway	SSR	NER	DNA_polymerase_delta
2071010	0.2921	0.2921	0.7597	0.7597	0.6366	0.6366	Repair_pathway	SSR	MMR	RFC_(replication_factor_C)
1051221	0.3184	0.3184	0.1559	0.1559	0.0106	0.0106	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	Other_single_Ring-_finger_type_E3
1010000	0.3225	0.3225	0.4385	0.4385	0.3231	0.3231	Associated_process	Chromatin_remodelling		
1051829	0.3284	0.3284	0.5913	0.5913	0.5578	0.5578	Associated_process	Ubiquitin_response	Ubiquitin-_activating_enzymes_(E1)	UBL-activating_enzymes
1051800	0.329	0.329	0.5913	0.5913	0.5578	0.5578	Associated_process	Ubiquitin_response	Ubiquitin-_activating_enzymes_(E1)	
1051927	0.3313	0.3313	0.7885	0.7885	0.4152	0.4152	Associated_process	Ubiquitin_response	Ubiquitin-_conjugating_enzymes_(E2)	Ubiquitin-conjugating_enzymes
3060000	0.3405	0.3405	0.1703	0.1703	0.3608	0.3608	Genes_with_probable_DDR_role	Direct_Repair_(not_in_humans)		
1031600	0.3856	0.3856	0.8438	0.8438	0.5119	0.5119	Associated_process	Telomere_maintenance	Alternative_mechanism	
1031616	0.3856	0.3856	0.8438	0.8438	0.5119	0.5119	Associated_process	Telomere_maintenance	Alternative_mechanism	MRN_Complex
2020200	0.4086	0.4086	0.6981	0.6981	0.5004	0.5004	Repair_pathway	DSR	HR_(Homologous_Recombination)	

1052000	0.42	0.42	0.3114	0.3114	0.4350	0.4350	Associated_process	Ubiquitin_response	Ubiquitins_and_Ubiquitin-like_proteins	
1052028	0.42	0.42	0.3114	0.3114	0.4350	0.4350	Associated_process	Ubiquitin_response	Ubiquitins_and_Ubiquitin-like_proteins	Ubiquitins
1000000	0.426	0.426	0.4378	0.4378	0.5759	0.5759	Associated_process			
1082500	0.4288	0.4288	0.1787	0.1787	0.5650	0.5650	Associated_process	Checkpoint_factors	FPC_(fork_protection_complex)	
2111531	0.43	0.43	0.2914	0.2914	0.2994	0.2994	Repair_pathway	Associated_process	TLS	Y-family_DNA_polymerases
2071018	0.4438	0.4438	0.2644	0.2644	0.2335	0.2335	Repair_pathway	SSR	MMR	MutS_homologs_specialized_for_meiosis
2110000	0.4479	0.4479	0.4485	0.4485	0.5960	0.5960	Repair_pathway	Associated_process		
2111500	0.4479	0.4479	0.4485	0.4485	0.5960	0.5960	Repair_pathway	Associated_process	TLS	
2020000	0.471	0.471	0.4388	0.4388	0.0835	0.0835	Repair_pathway	DSR		
1050500	0.4757	0.4757	0.8548	0.8548	0.8561	0.8561	Associated_process	Ubiquitin_response	Deubiquitinating_enzyme_(DUB)	
1050501	0.4757	0.4757	0.8548	0.8548	0.8561	0.8561	Associated_process	Ubiquitin_response	Deubiquitinating_enzyme_(DUB)	UBL-specific_proteases_(ULPs)
1080000	0.4863	0.4863	0.4497	0.4497	0.8204	0.8204	Associated_process	Checkpoint_factors		
2072800	0.4971	0.4971	0.5818	0.5818	0.0702	0.0702	Repair_pathway	SSR	Other_SSR_genes	
2020400	0.5069	0.5069	0.7838	0.7838	0.8179	0.8179	Repair_pathway	DSR	NHEJ	
2071100	0.5175	0.5175	0.1144	0.1144	0.2760	0.2760	Repair_pathway	SSR	BER	
1082600	0.5196	0.5196	0.5642	0.5642	0.6168	0.6168	Associated_process	Checkpoint_factors	G2-CC_phase	
1090000	0.5699	0.5699	0.567	0.567	0.6151	0.6151	Associated_process	p53_pathway		
1050000	0.5879	0.5879	0.3435	0.3435	0.2168	0.2168	Associated_process	Ubiquitin_response		
2070602	0.593	0.593	0.1607	0.1607	0.3081	0.3081	Repair_pathway	SSR	NER	GGR_(Global_genome_repair)
2020300	0.6054	0.6054	0.5235	0.5235	0.6240	0.6240	Repair_pathway	DSR	Other_DSR_genes	
2071119	0.6093	0.6093	0.06716	0.06716	0.9067	0.9067	Repair_pathway	SSR	BER	Other_BER_factors
2071111	0.6105	0.6105	0.2266	0.2266	0.5242	0.5242	Repair_pathway	SSR	BER	AP_endonucleases
1082700	0.6144	0.6144	0.6852	0.6852	0.9253	0.9253	Associated_process	Checkpoint_factors	G2-M_checkpoint	
2021400	0.6216	0.6216	0.04964	0.04964	0.1448	0.1448	Repair_pathway	DSR	HR_(HomologousRecombination)	
1051700	0.642	0.642	0.461	0.461	0.5626	0.5626	Associated_process	Ubiquitin_response	Ubiquitin-like_proteins_(UBLs)	
1051725	0.642	0.642	0.461	0.461	0.5626	0.5626	Associated_process	Ubiquitin_response	Ubiquitin-like_proteins_(UBLs)	SUMO
1051200	0.6607	0.6607	0.07437	0.07437	0.0558	0.0558	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	
1082900	0.6626	0.6626	0.8717	0.8717	0.8865	0.8865	Associated_process	Checkpoint_factors	Rad17-Mec3-_Ddc1_complex	
1082200	0.6692	0.6692	0.08041	0.08041	0.2304	0.2304	Associated_process	Checkpoint_factors	damage_in_S_phase	
2111514	0.7197	0.7197	0.5245	0.5245	0.7104	0.7104	Repair_pathway	Associated_process	TLS	epistasis_group

2020100	0.7228	0.7228	0.5406	0.5406	0.5703	0.5703	Repair_pathway	DSR	FA_(Fanconi_anemia_pathway)	
1040000	0.7462	0.7462	0.5933	0.5933	0.6618	0.6618	Associated_process	Chromosome_segregation		
3000000	0.7855	0.7855	0.6186	0.6186	0.3003	0.3003	Genes_with_probable_DDR_role			
2072300	0.7965	0.7965	0.3243	0.3243	0.8883	0.8883	Repair_pathway	SSR	Direct_Repair	
2072400	0.8269	0.8269	0.00389	0.003891	0.0687	0.0687	Repair_pathway	SSR	DNA_replication	
2071124	0.8385	0.8385	0.894	0.894	0.8192	0.8192	Repair_pathway	SSR	BER	SHORT_PATCH-BER_factors
2071112	0.9015	0.9015	0.1669	0.1669	0.3575	0.3575	Repair_pathway	SSR	BER	DNA_glycosylases
1051209	0.9247	0.9247	0.01381	0.01381	0.0559	0.0559	Associated_process	Ubiquitin_response	Ubiquitin_ligases_(E3)	single_Ring-finger_type_E4
1120000	0.9579	0.9579	0.6229	0.6229	0.9969	0.9969	Associated_process	Modulation_of_nucleotide_pools		
1083000	0.9619	0.9619	0.7832	0.7832	0.9161	0.9161	Associated_process	Checkpoint_factors	RAD9-Hus1-Rad1_complex	

Supplementary Table 20: Distribution of progression measure in 218 members of TRACK-HD cohort, showing numbers and percentage of TRACK-HD cohort in each bin of the histogram shown in Figure 2C.

Bin midpoint	Observed percent	Number (total = 218)
-3	0.054	1
-2.5	0.109	2
-2	1.798	33
-1.5	4.796	88
-1	11.717	215
-0.5	17.057	313
0	21.907	402
0.5	22.016	404
1	14.114	259
1.5	4.85	89
2	1.308	24
2.5	0.272	5

Supplementary Table 21: Distribution of atypical severity (compared to predicted severity at final visit) in in 1835 members of the REGISTRY cohort, showing numbers and percentage of REGISTRY cohort in each bin of the histogram shown in Figure 2D.

Bin midpoint	Observed percent	Number (total = 1835)
-2.5	1.376	3
-2	1.376	3
-1.5	4.128	9
-1	15.596	34
-0.5	21.56	47
0	18.807	41
0.5	17.89	39
1	9.633	21
1.5	4.587	10
2	1.835	4
2.5	2.294	5
3	0.459	1
3.5	0	0
4	0.459	1