Supplementary Information for "Huntington's disease age at motor onset is modified by the tandem hexamer repeat in *TCERG1*"

Supplementary Tables

Regression	$\mathcal{R}_{thr}$	N_{early}	N_{late}	Sum		Max		Min		Diff	
				b	*p*	b	*p*	b	*p*	b	*p*
Linear	Not applicable			-2.74	5.0E-09	-3.75	1.2E-03	-2.85	1.8E-07	1.82	4.9E-04
Logistic	0	323	287	-0.45	7.7E-08	-0.66	1.9E-03	-0.45	2.1E-06	0.27	1.9E-03
	7	238	203	-0.48	8.9E-07	-0.86	1.3E-03	-0.47	1.8E-05	0.28	5.9E-03
	13	149	78	-0.83	2.0E-09	-66.68	7.1E-04	-0.84	1.7E-08	0.65	5.0E-06
	20	24	11	-35.73	3.2E-05	-51.33	7.9E-02	-34.71	3.9E-05	1.37	5.1E-04

Supplementary Table 1. Significance of the association between TCERG1 exon 4 quasi-tandem repeat (QTR) and residual age at onset $\mathcal{R}$ for the various ways of coding the repeat. Blue and red colours highlight numbers passing 10^{-5} and $5 \cdot 10^{-8}$ *p*-value thresholds for significance, respectively.

$\mathcal{R}_{thr}$: residual age at onset threshold used for logistic regression (years)

$\mathbb{N}_{early}$: number of people with early onset used for logistic regression who have $\mathcal{R} < -\mathcal{R}_{thr}$

$\mathbb{N}_{late}$: number of people with late onset used for logistic regression who have $\mathcal{R} > \mathcal{R}_{thr}$

Max: QTR repeat length of the longest allele N_{max}

Min: QTR repeat length of the shortest allele N_{min}

Sum: sum of two QTR repeat lengths $N_{sum} = N_{max} + N_{min}$

Diff: difference of two QTR lengths $N_{diff} = N_{max} - N_{min}$

Cohort	Type of regression analysis of REGISTRY	b	SE	CI		*p*
REGISTRY	Linear	-3.10	0.55	-4.19	-2.02	3.15E-08
	Selection	-0.98	0.19	-1.36	-0.62	2.30E-08
Predict-HD	N/A	-1.26	0.56	-2.37	-0.14	0.027
Combined	Linear	-2.74	0.46	-3.65	-1.84	5.02E-09
	Selection	-1.00	0.18	-1.37	-0.67	2.14E-09

Supplementary Table 2. Significance of the association between the sum of TCERG1 QTR lengths and residual age at onset in REGISTRY, Predict-HD and combined samples. Two types of regression analysis of the REGISTRY cohort are presented: linear regression analysis and regression with selection (see Supplementary Methods section below).

Regression	$\mathcal{R}_{thr}$	N_{early}	N_{late}	Sum		Max		Min		Diff	
				b	*p*	b	*p*	b	*p*	b	*p*
Linear	Not applicable			-2.75	6.5E-09	-3.78	1.2E-03	-2.85	2.4E-07	1.80	6.5E-04
Logistic	0	323	287	-0.45	1.2E-07	-0.64	2.5E-03	-0.45	2.7E-06	0.27	2.0E-03
	7	238	203	-0.48	1.1E-06	-0.86	1.3E-03	-0.47	2.3E-05	0.28	7.4E-03
	13	149	78	-0.83	2.8E-09	-66.68	7.1E-04	-0.85	2.3E-08	0.65	7.3E-06
	20	24	11	-35.73	3.2E-05	-51.33	7.9E-02	-34.71	3.9E-05	1.37	5.1E-04

Supplementary Table 3. As **Supplementary Table 1**, but for short tandem repeat (STR).

Baseline model	Additional statistic				
	Sum	Max	Min	Diff	#3 repeats
Sum	X	0.79	0.79	0.79	0.67
Max	1.07E-06	X	1.07E-06	1.07E-06	3.33E-05
Min	8.28E-03	8.28E-03	X	8.28E-03	0.71
Diff	2.61E-06	2.61E-06	2.61E-06	X	6.03E-03
#3repeats	1.29E-04	4.77E-03	5.49E-03	0.95	X

Supplementary Table 4. Significance (p-value) of improvement in fit to residual age at onset given by adding the "additional" QTR statistic to a model containing the "baseline" QTR statistic. See **Supplementary Table 1** for explanation of Sum, Max, Min, and Diff.

Supplementary Data

eQTLGen-PPP2R2B. List of significant eQTLGen eQTLs for PPP2R2B with corresponding p-value for association with age at onset in the GeM GWAS. “P-value” = eQTLGen eQTL p-value, “Z-score” = eQTLGen test statistic. Positive Z means that the “assessed” allele is associated with higher expression. “AAO_effect” is the increase (or decrease, if negative) in age at onset (years) associated in the GeM GWAS with one copy of the “assessed” allele. P(GeM) is the p-value for association with age at onset in the GeM GWAS.

eQTLGen-TCERG1. List of significant eQTLGen eQTLs for TCERG1 with corresponding p-value for association with age at onset in the GeM GWAS. “P-value” = eQTLGen eQTL p-value, “Z-score” = eQTLGen test statistic. Positive Z means that the “assessed” allele is associated with higher expression. “AAO_effect” is the increase (or decrease, if negative) in age at onset (years) associated in the GeM GWAS with one copy of the “assessed” allele. P(GeM) is the p-value for association with age at onset in the GeM GWAS.

PsychENCODE-TCERG1. List of significant psychENCODE eQTLs for TCERG1 with corresponding p-value for association with age at onset in the GeM GWAS. “eQTL_pval” = psychENCODE eQTL p-value, “eQTL_effect” = change in expression associated with each copy of allele A1. “AAO_effect” is the increase (or decrease, if negative) in age at onset (years) associated in the GeM GWAS with one copy of the “assessed” allele. P(GeM) is the p-value for association with age at onset in the GeM GWAS.

PsychENCODE-PPP2R2B. List of significant psychENCODE eQTLs for PPP2R2B with corresponding p-value for association with age at onset in the GeM GWAS. “eQTL_pval” = psychENCODE eQTL p-value, “eQTL_effect” = change in expression associated with each copy of allele A1. “AAO_effect” is the increase (or decrease, if negative) in age at onset (years) associated in the GeM GWAS with one copy of the “assessed” allele. P(GeM) is the p-value for association with age at onset in the GeM GWAS.

Supplementary Figures

MAERGGDGGESERFNPGELRMAQQQALRFRGPAPPPNAVMRGPPPLMRPPPPFGMMRGPPPPPRPPFGRP
PFDPNMPPMPPPGGIPPPMGPPHLQRPPFMPPPMSSMPPPPGMMFPPGMPPVTAPGTPALPPTEEIWVEN
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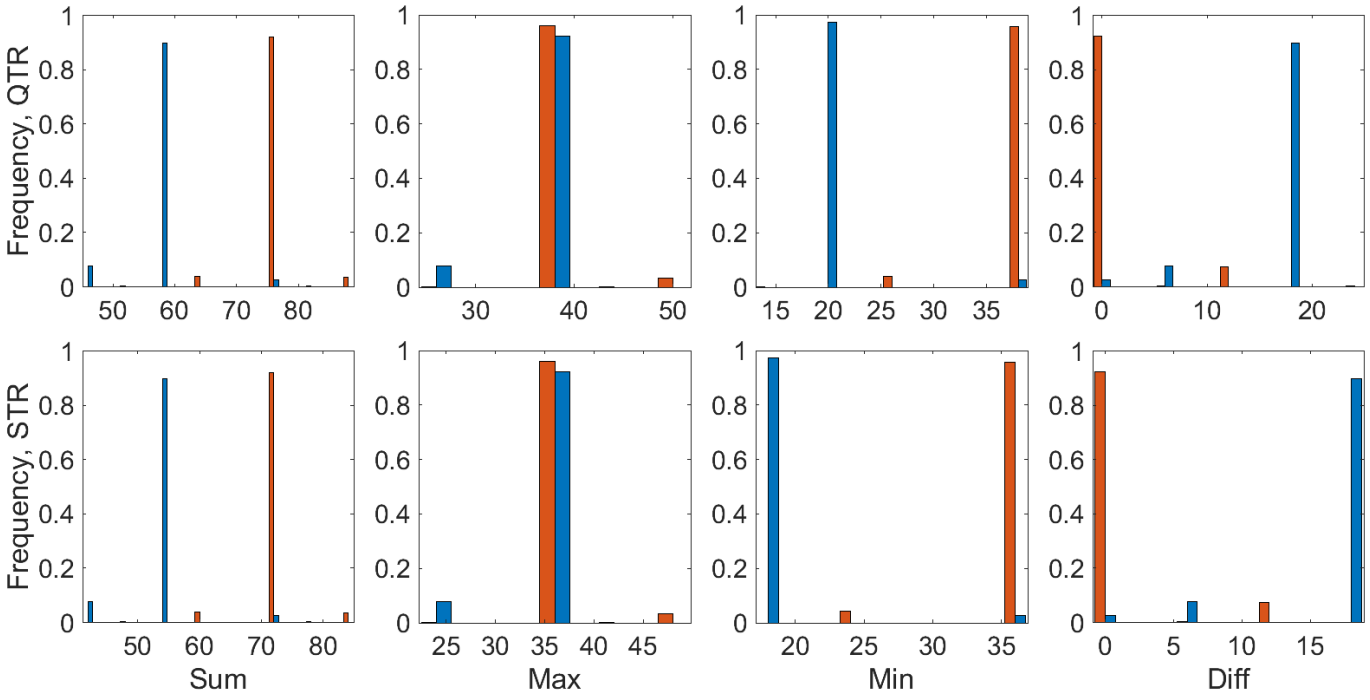
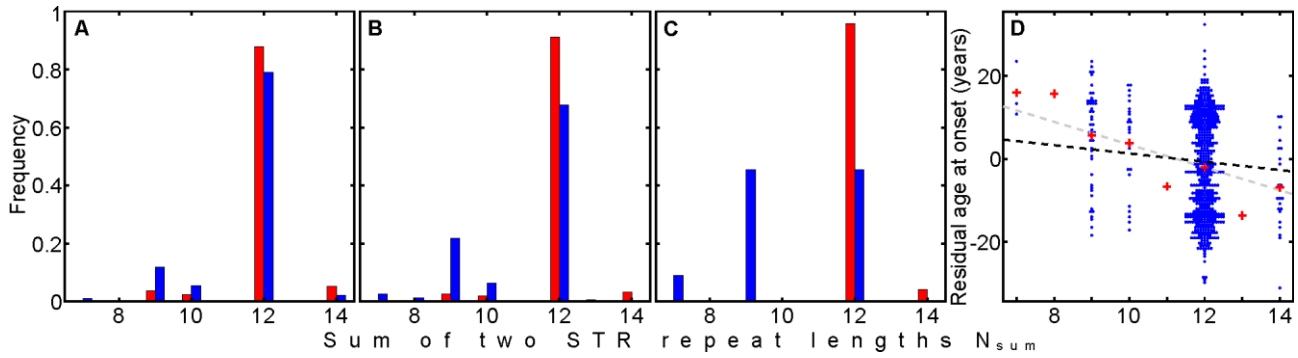
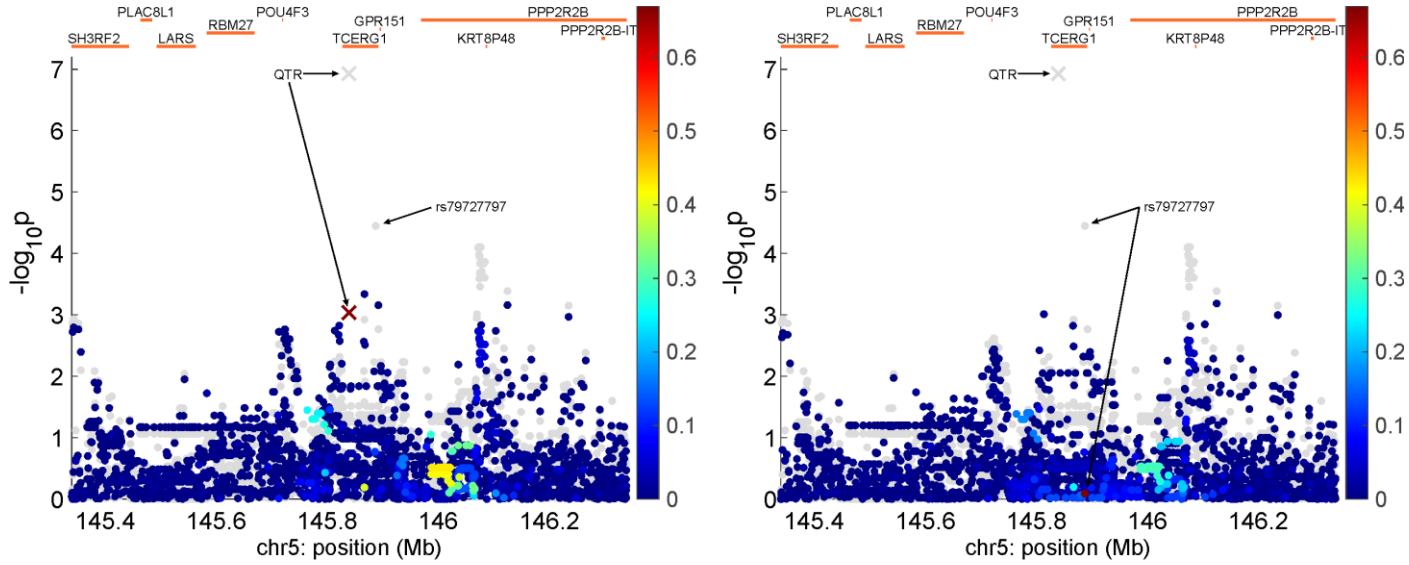
Supplementary Figure 1. Transcription elongation regulator 1 isoform 3 [Homo sapiens]. NCBI Reference Sequence: NP_001369477.1



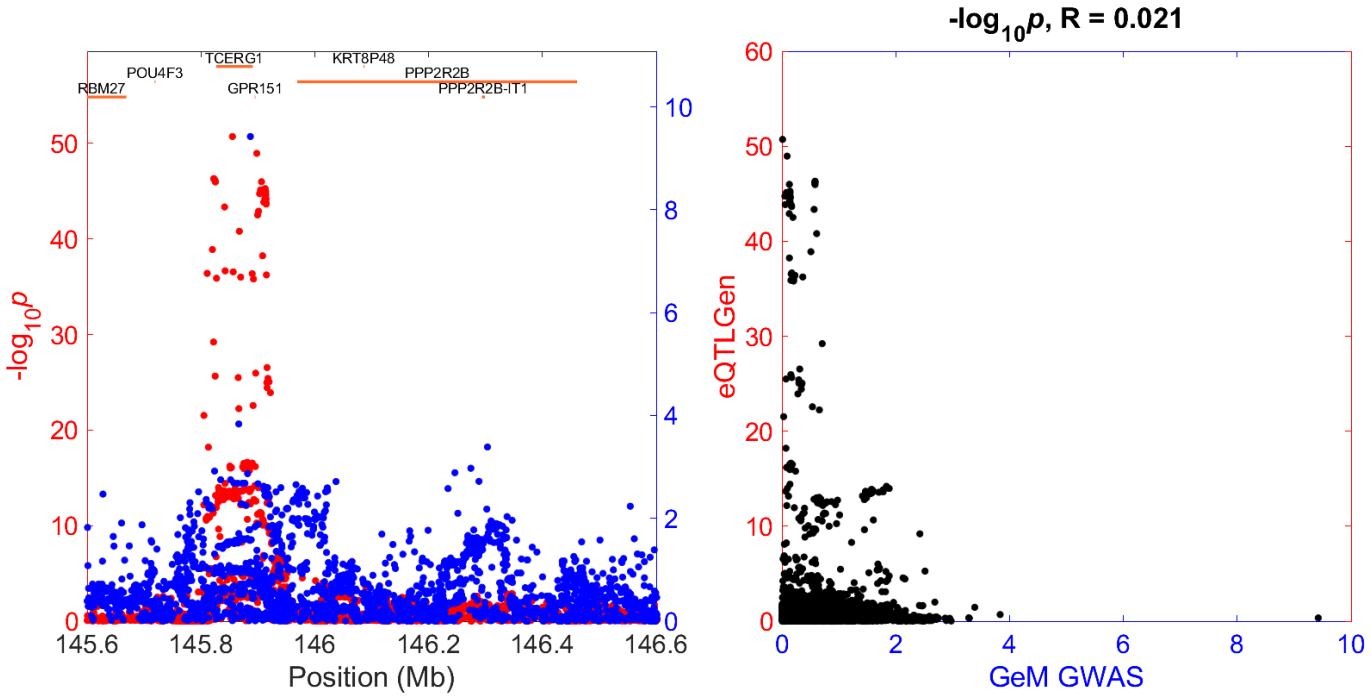
Supplementary Figure 2. Plots of the distribution of QTR (top) and STR (bottom) lengths in individuals with 0 (red) and 1 (blue) minor alleles at rs79727797 for the 468 individuals with both SNV and sequencing data. See **Supplementary Table 1** for explanation of Sum, Max, Min, and Diff.



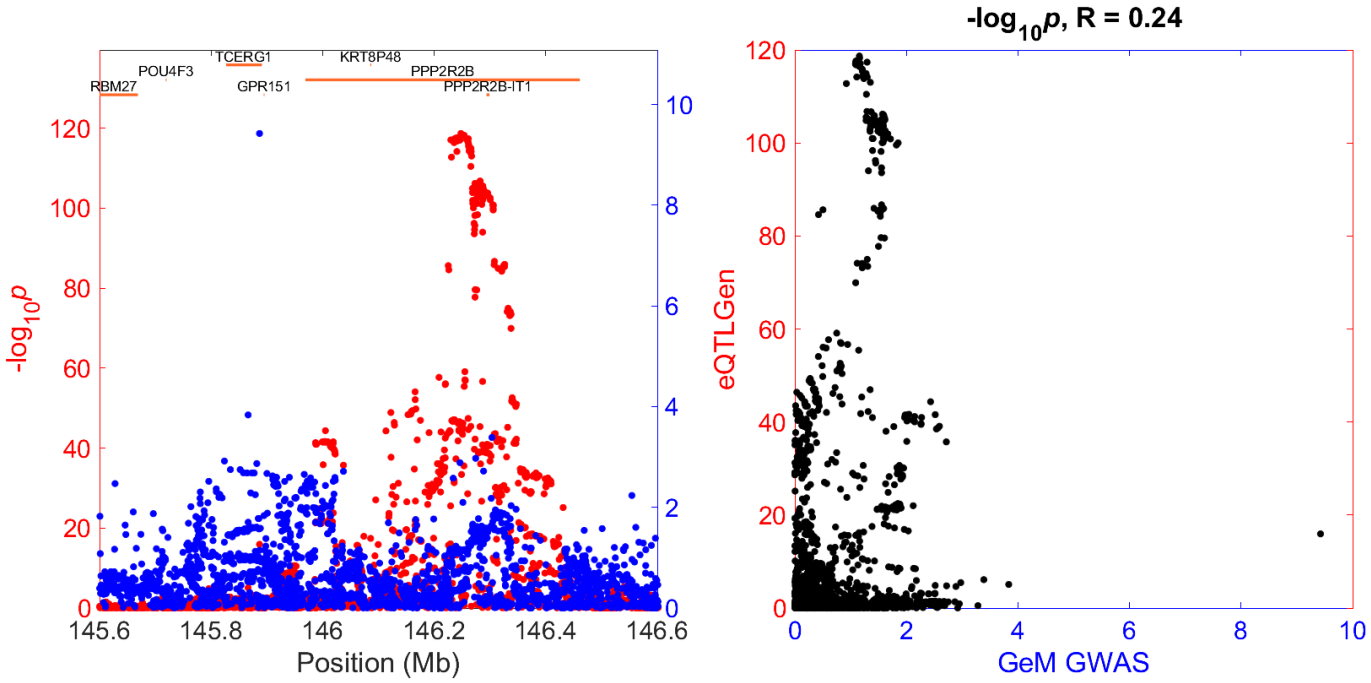
Supplementary Figure 3. The relationship between hexanucleotide short tandem repeat (STR) length and residual age at onset of HD. **a-c** Histograms showing distribution of the sum of two STR repeat lengths $N_{sum} = N_{min} + N_{max}$ for the groups with early (red, $R<-R_{thr}$) and late (blue, $R>R_{thr}$) onsets. The panels **a**, **b**, and **c** correspond to the residual age at onset threshold R_{thr} of 0, 13, and 20 years, respectively. **d** Association of the sum of two STR repeat lengths N_{sum} with the residual age at onset for the entire HD cohort. Red pluses indicate mean residual age at onset for every sum of STR repeat lengths. Grey and black dashed lines are plotted using coefficients of the linear regression analysis and regression with selection.



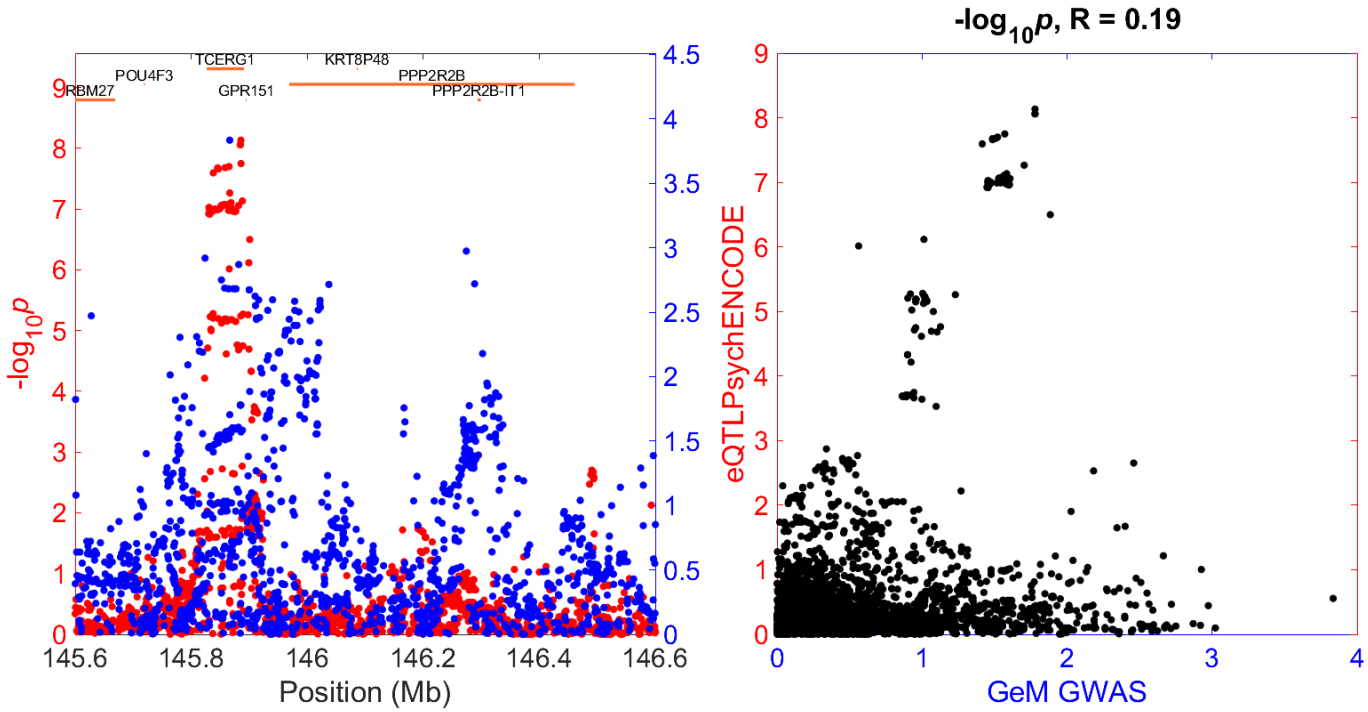
Supplementary Figure 4. Manhattan plots of residual age at onset association conditioning on rs79727797 (left panel) and QTR (right panel) for 468 HD individuals with both sequencing and GWAS data. The bar on the right of the plots indicates the strength of linkage disequilibrium (r2) between each SNP/QTR and the variant being conditioned on. The grey dots mark p-values prior to conditioning. The variant being conditioned on necessarily disappears from the plot.



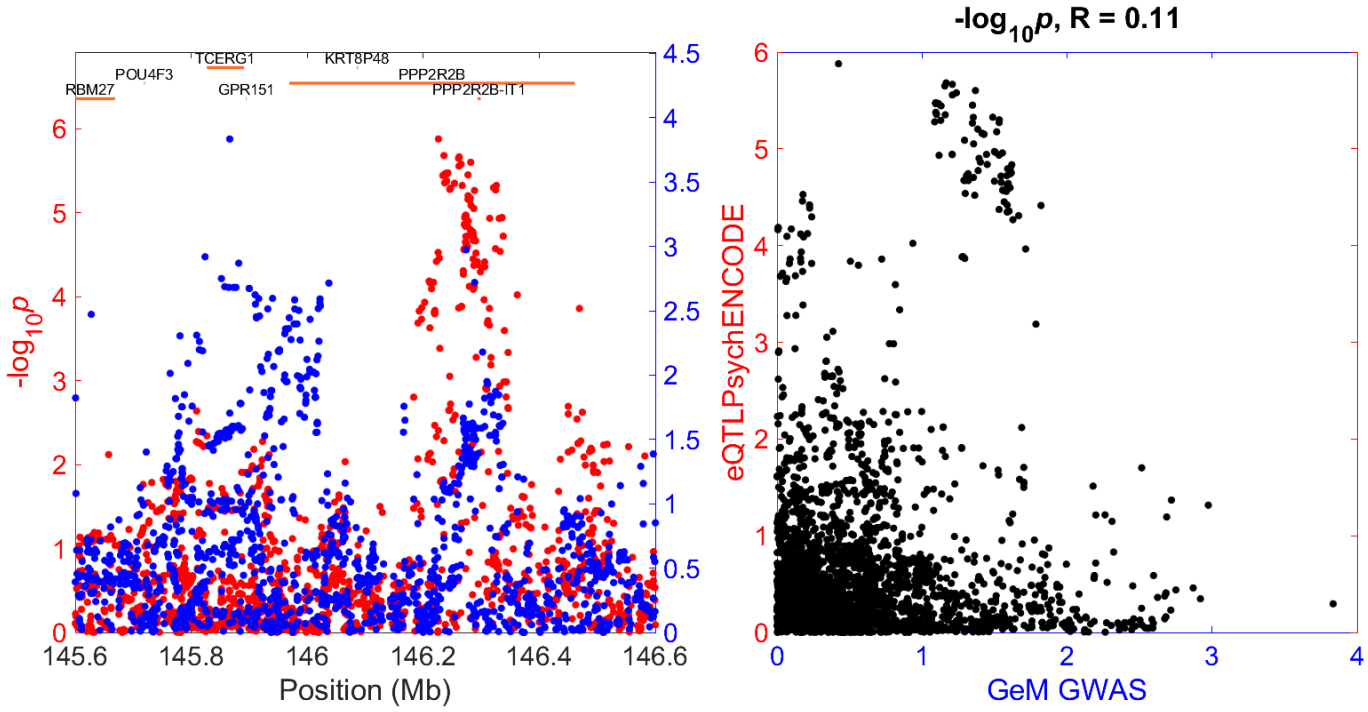
Supplementary Figure 5. Plots of TCERG1 eQTL -log p-value from eQTLGen (red) and GeM GWAS -log p-value (blue) vs chromosome position (left panel) and each other (right panel)



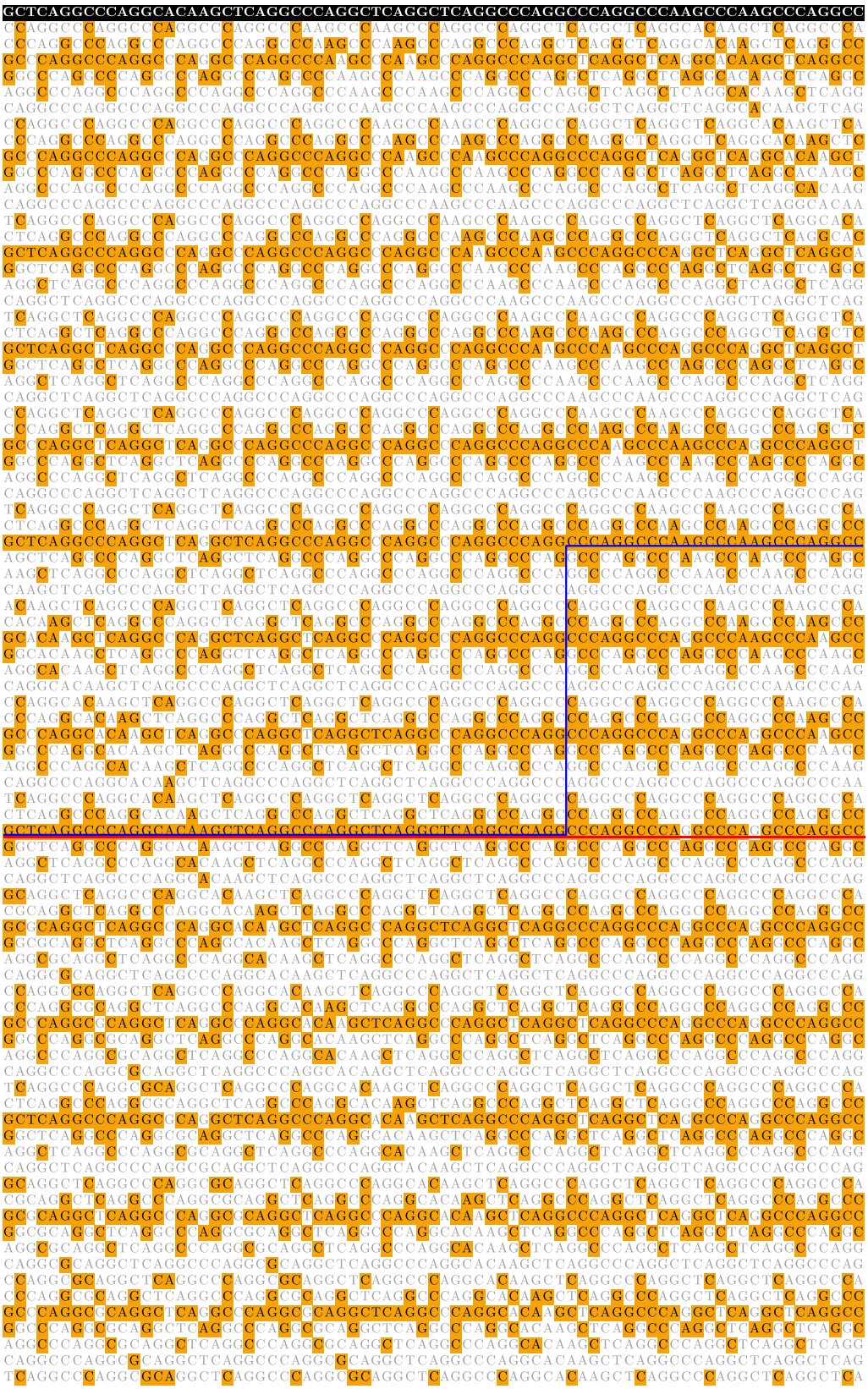
Supplementary Figure 6. Plots of PPP2R2B eQTL -log p-value from eQTLGen (red) and GeM GWAS -log p-value (blue) vs chromosome position (left panel) and each other (right panel)



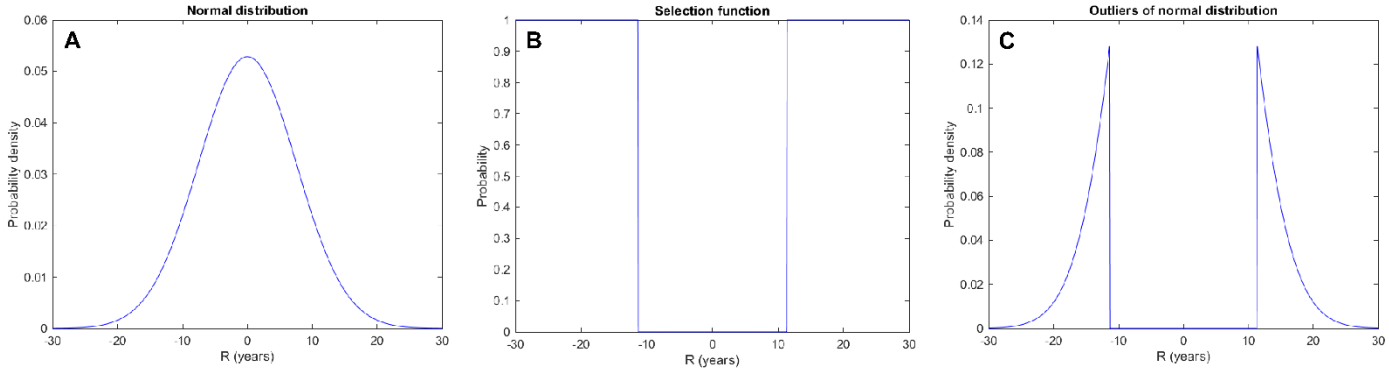
Supplementary Figure 7. Plots of TCERG1 eQTL -log p-value from PsychENCODE (red) and GeM GWAS -log p-value (blue) vs chromosome position (left panel) and each other (right panel)



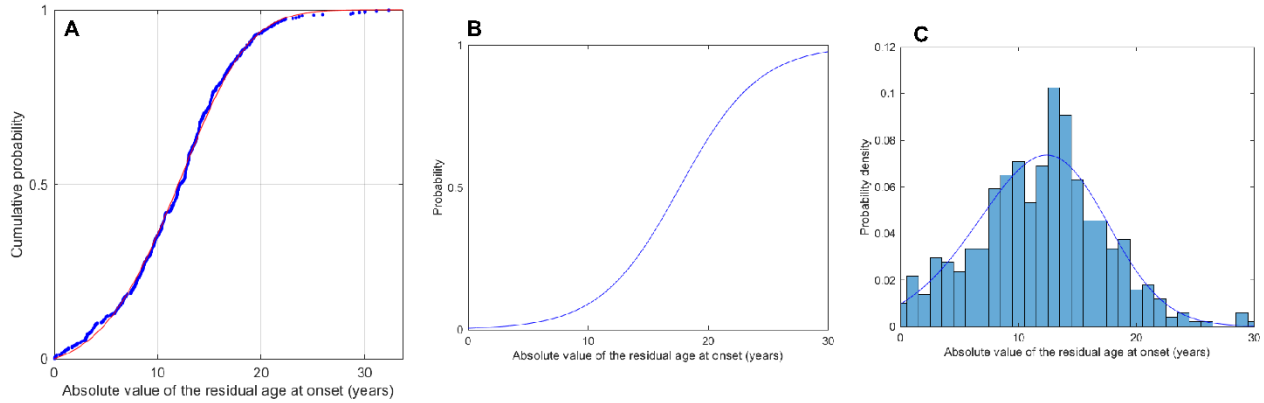
Supplementary Figure 8. Plots of PPP2R2B eQTL -log p-value from PsychENCODE (red) and GeM GWAS -log p-value (blue) vs chromosome position (left panel) and each other (right panel)



Supplementary Figure 9. Illustration of the match matrix. The top line with white letters on a black ground specifies the nucleotide sequence of a read. Other lines represent nucleotide sequences of the reference genome shifted by one nucleotide with respect to the previous (upper) line. Matched nucleotides are highlighted with a yellow colour which creates the match matrix (yellow = True, white = False). Two read alignments are shown. The naive way to align a read with two mismatched nucleotides is shown as a red straight line. The path with one deletion, which takes into account the highly mutative nature of STRs/QTRs, is shown with a blue line.



Supplementary Figure 10. **a** Expected probability density of the initial HD population (normal distribution); **b** Selection function with infinitely small Δ; **c** Expected probability density of the small HD sub-group with largest absolute value of the residual age at onset $|R|$.



Supplementary Figure 11. **a** The observed (blue dots) and expected (red line) cumulative probabilities; **b** The selection function with optimal parameters; **c** The observed (bars) and expected (line) probability densities.

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