A modifier of Huntington's disease onset at the *MLH1* locus

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Abstract

Huntington's disease (HD) is a dominantly inherited neurodegenerative disease caused by an expanded CAG repeat in *HTT*. Many clinical characteristics of HD such as age at motor onset are determined largely by the size of *HTT* CAG repeat. However, emerging evidence strongly supports a role for other genetic factors in modifying the disease pathogenesis driven by mutant huntingtin. A recent genome-wide association analysis to discover genetic modifiers of HD onset age provided initial evidence for modifier loci on chromosomes 8 and 15 and suggestive evidence for a locus on chromosome 3. Here, genotyping of candidate SNPs in a cohort of 3,314 additional HD subjects yields independent confirmation of the former two loci and moves the third to genome-wide significance at *MLH1*, a locus whose mouse orthologue modifies CAG length-dependent phenotypes in a *Htt*-knock-in mouse model of HD. Both quantitative and dichotomous association analyses implicate a functional variant on ~32% of chromosomes with beneficial modifier effect that delays HD motor onset by 0.7 years/allele. Genomic DNA capture and sequencing of the modifier haplotype localize the functional variation to a 78 kb region spanning the 3'end of *MLH1* and the 5'end of the neighboring *LRRFIP2*, and marked by an isoleucine-valine missense variant in *MLH1*. Analysis of eQTLs provides modest support for altered regulation of *MLH1* and *LRRFIP2,* raising the possibility that the modifier affects regulation of both genes. Finally, polygenic modification score and heritability analyses suggest the existence of additional genetic modifiers, supporting expanded, comprehensive genetic analysis of larger HD datasets.

Introduction

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder in which an unstable expanded CAG trinucleotide repeat of > 35 units in *HTT,* the 4p16.3 gene encoding huntingtin (1), precipitates a characteristic movement disorder and premature death (2, 3). The length of the CAG expansion is the primary determinant of the rate of the HD disease process since its size is inversely correlated with the age at onset of neurologic symptoms (4-8). However, other genetic factors also play a role in influencing the time to onset (9, 10). A recent genome-wide association (GWA) analysis of the difference between actual and CAG-predicted age at onset in ~4,000 HD individuals identified genome-wide significant modifier loci, one with two independent modifier signals on chromosome 15 and a single modifier signal on chromosome 8 (11). In addition, a suggestive association signal was detected in chromosome 3p22.2 near *mutL homolog 1* (*MLH1*) (11), known for its involvement in DNA mismatch repair (12). Dominant loss of function mutation of *MLH1* are associated with Lynch Syndrome (Hereditary Non-Polyposis Colon Cancer type 2 or HNPCC2; MIM#609310), in which tumors display instability of dinucleotide repeats. The 3p22 GWA signal in our study contributed to pathway analyses that further highlighted a role for DNA maintenance processes in HD modification, supporting the hypothesis that somatic CAG instability may influence onset age suggested previously by a correlation between high instability of the expanded repeat in HD postmortem brain tissue and an earlier age at motor onset (13). Moreover, genetic ablation of the murine *MLH1* homolog, *Mlh1,* in *Htt* CAG repeat knock-in mice eliminated instability of the expanded repeat and ameliorated nuclear huntingtin staining, a striatal disease phenotype (14). To obtain independent confirmation of the loci on chromosomes 8 and 15 and to test the significance of several other potential modifier loci, especially that in 3p22.2, we employed the Fluidigm platform to genotype individual

candidate SNPs in a large independent cohort of HD individuals: 3,314 participants from the European Huntington's Disease Network (EHDN) Registry collection.

Results

Single SNP association analysis reveals a 3rd genome-wide significant modifier locus

Study subjects analyzed here displayed distributions of age at onset corrected for CAG repeat size (i.e., residual age at onset) and minor allele frequencies (MAF) comparable to the previous GWA samples (Figures S1-S2). A number of the top scoring SNPs from the original GWA study (11, 15) were not suitable for the Fluidigm genotyping platform (https://www.fluidigm.com/), so we substituted other variants that captured the same modifier signals. Ultimately, we genotyped the replication set for rs34852161 at the chromosome 8 locus, rs150393409 and rs35811129 representing independent modifier effects in the same region of chromosome 15, rs116483964 and rs1799977 at the 3p22.2 locus and individual SNPs at 57 additional loci chosen for being amenable to the platform and having a p-value < 0.005 in either quantitative or dichotomous analysis from the original GWA (11) (Table S1). Quantitative association analysis using residual age at motor onset as the phenotype revealed nominally significant scores for rs34852161 on chromosome 8 and rs150393409 on chromosome 15, while rs35811129 on chromosome 15 yielded genome-wide significance (p-value 2E-10) in the replication set (Table 1; Table S2). In meta-analysis with the prior GWA study, all three yielded genome-wide significant scores, confirming the modifier effects reported previously (11). At the 3p22.2 locus, both rs1799977 in *MLH1* and rs116483964 in the adjacent *LRRFIP2* exhibited nominally significant p-values (Table 1). Meta-analysis

combining the replication data and GWA analysis results raised both to genome-wide significance (8.84E-09 and 1.19E-08, respectively) (Table 1; Figure 1A, filled red circles).

As this finding adds an additional locus to the list of genome-wide significant HD modifiers, we also carried out dichotomous analysis to evaluate the possibility that the significant association in quantitative analysis was driven by a few individuals with extreme residuals. Comparison of allele frequencies between the top and bottom 20% phenotypic extreme samples from the combined data (1,478 samples for each extreme group) also revealed genome-wide significance for rs1799977 (p-value, 5.3E-09) and rs116483964 (p-value, 5.6E-09) (Table 2A). Conditional analysis demonstrated that both SNPs appear to capture a single modifier effect (Table 2B). The minor allele of each SNP was associated with delaying age at onset by approximately 0.7 years, explaining 0.5% of the residual age at onset in the combined data set. Of the remaining 57 independent loci tested, none attained genome-wide significance in the meta-analysis of GWA and Fluidigm data sets, although 3 were nominally significant (p-value < 0.05) in the latter (Table S2).

Narrowed localization of the Chr3 functional variation responsible for modification of HD

The rs1799977 minor allele is a missense (isoleucine to valine) variant in *MLH1*, with a reported allele frequency of about 32.5% in 1,000 Genomes Project Europeans. As noted above, *MLH1* is involved in DNA mismatch repair (12, 16) and HD CAG repeat instability (14), and inactivating mutations are present in some Lynch Syndrome families (17). SNP rs116483964, with a comparable minor allele frequency, is in an early intron of the immediately adjacent gene, *LRRFIP2,* whose product, Leucine Rich Repeat (In FLII) Interacting Protein 2, is involved in protein-protein interactions that regulate Wnt-signaling (18). *LRRFIP2* is deleted together with

MLH1 as a founder mutation in some Portuguese Lynch syndrome families (19). In the original GWA study, there were other SNPs with comparable p-values at this locus that were not amenable to genotyping on the Fluidigm platform. To seek the variation responsible for the modifier effect, we selected 7 unrelated HD subjects homozygous for the minor allele of rs144287831, the top SNP from the GWA analysis (11), and with positive age of onset residuals > 4, and performed genomic DNA capture and sequencing of the 771 kb region (Figure 1A, a blue horizontal bar; Chr3:36,832,273-37,603,667) spanning *TRANK1, EPM2AIP1, MLH1, LRRFIP2, GOLGA4, C3orf35* and a portion of *ITGA9*. These 14 chromosomes from 7 HD individuals were near identical for all frequent (> 1%) reported SNPs across a haplotype of approximately 100 kb between Chr3:37,043,009-37,142,847 (Figure 1A, a red horizontal bar; Table S3). Encompassed by this haplotype were the minor alleles for the 7 top scoring markers from the GWA, all of which have a frequency of 0.31 - 0.32 in our HD dataset (Table 3). Each of these markers shows a striking shift of the minor allele toward the 4^{th} quartile of the age of onset residual distribution, indicative of a contribution of a chromosome bearing this 7-marker haplotype to later than expected onset (Table 3).

The GWA and capture sequencing data both argue that 0.31 - 0.32 is the frequency of the responsible functional modifier variation at this locus in European HD subjects. First, the 100 kb shared haplotype also contains many polymorphic sites of higher MAF (107 sites MAF > 0.32) in Europeans, but these all yielded weaker significance scores in both quantitative and dichotomous association analysis (Figure 1B, filled grey circles), indicating that signal from the allele on the modifier haplotype is diluted by the presence of the same allele on many non-modifier chromosomes. Second, all markers with MAF < 0.31 (70 sites with MAF > 0.02) yielded weaker

significance scores in the GWA analysis (Figure 1B, open grey circles), indicating that they did not fully capture the modifier effect and arguing against the effect being contributed by only a subset of the chromosomes marked by the top SNPs. Finally, our capture sequencing of these 14 candidate modifier chromosomes did not identify any shared novel variants that could be responsible for modification (Table S3). Consequently, the modifier effect is likely to be due to one or more of the markers listed in Table 3, acting either individually or together through part or all of the haplotype that they define. Although we cannot completely exclude an undetected structural variation or a change in a simple sequence repeat, as these may remain cryptic to the capture sequencing used, we did exclude the presence of structural variations greater than a few kb using whole genome sequencing of large-insert jumping libraries (20, 21). The most attractive candidate variant is rs1799977 since it alters the primary sequence of the MLH1 protein, may impact mildly on its interaction with PMS2 (22) and has been associated with allelic expression of the *MLH1* transcript (23). The ancestral A allele of rs1799977 specifies an isoleucine residue at position 219 that is conserved across mammals. The alternate G allele specifies valine, which is present in this conserved region of the MLH1 proteins of some reptiles, birds, fish and lower organisms, consistent with a functional but subtly different MLH1 protein. In candidate studies, this I219V polymorphism has been tested as a low penetrance risk factor or modifier of various cancers, with mixed results, again suggestive of only a subtle functional impact (24-32). Neither rs1799977 nor the other SNPs in the modifier haplotype are listed in the GWAS catalog (2017-02-13 release) as associated with genome-wide significance to cancer or other human phenotypes.

Potential effect of the modifier haplotype on gene expression

The two Chr3 markers used here both yielded significant eQTL signals with expression of multiple genes in the region (*MLH1, LRRFIP2,* and *GOLGA4)* in various tissues (GTEx portal, V6; http://www.gtexportal.org/home/). To examine whether the modifier haplotype contributes to any *cis*-eQTLs, we related the association signals for all GWA SNPs in the Chr3:36,800,000-37,800,000 region (Figure 1) to eQTL signals for the local genes. We employed the HaploReg annotation tool (http://archive.broadinstitute.org/mammals/haploreg/haploreg.php) to determine the number of tissues in which the test SNP was significantly associated with expression of the test gene. The results revealed only modest correspondence between GWA modifier association signals and HaploReg eQTL data for *MLH1* and a mildly stronger correspondence for *LRRFIP2,* but no correspondence for other genes in the region (Figure S3). When we directly compared the strength of the GWA modifier association signal for each SNP with that of its eQTL signal in the GTEx database (Figure S4), we found a significant correlation between eQTL signals for *LRRFIP2* in putamen and modifier association signals (Figure S4B, top right panel; Pearson's correlation, p-value < 2.2E-16). In an independent data set (BRAINEAC; http://www.braineac.org/), we did not see a significant eQTL association for *MLH1* or *LRRFIP2*, but did observe correlated relationships between exon level QTL signals and modification signals for certain regions of *LRRFIP2* (Figure S5). The modifier haplotype was associated with increased levels of *LRRFIP2* but not *MLH1* mRNA in brain tissues, but this gene-level analysis does not account for different transcript isoforms or address all brain regions (Figure S6; rs1799977). It remains uncertain which particular cell type is responsible for the modifier effect and whether there is a coincident impact on expression of any *MLH1* transcript isoform. Notably, one rare transcript isoform of *MLH1* is reported to overlap with *LRRFIP2,* suggesting the possibility that regulatory changes could in

some instances affect expression of both genes. More detailed molecular studies in human HD tissues will be required to determine the precise impact(s) of this modifier haplotype on both *MLH1* and *LRRFIP2*.

Genetic component of residual age at onset

The four independent genome-wide significant modifier signals at 3 loci explain only a small portion of the variance in residual HD age at onset. Therefore, we evaluated the explanatory power of a polygenic modification score to determine the degree to which residual age at onset is better accounted for by a composite genetic score that includes many nominally associated SNPs. Overall, the effect sizes of 61 independent SNPs (only rs1799977 was used to represent 3p22.2) in the GWA data and in the replication samples were not significantly different (sign test p-value, 0.609). Based upon effect sizes of SNPs estimated from the GWA analysis as a training set, a polygenic modification score was calculated for each of the 3,314 individuals in the Fluidigm data set. Then, residual age at onset was modeled as a function of polygenic modification score from the Fluidigm data. All 61 independent SNPs (one SNP for chromosome 3 and 60 other independent SNPs) were significant in the original GWA data (nominal p-value < 0.05) (Table S2), and the subsequently derived polygenic modification score explained a nominally significant amount of the variance in residual age at onset of the Fluidigm samples (p-value, 0.0157). Although somewhat biased, the polygenic modification score based on the Fluidigm samples (using SNPs with nominal p-value < 0.05) was highly significant in accounting for residual age at onset in HD subjects in the GWA data (p-value, 4.0E-26). When those missing genotypes in the Fluidigm test data set were assigned an expected genotype based upon allele frequency, the modification score became slightly more significant (Table S4), suggesting that missing genotypes and the smaller

size of test sample might have contributed to sub-optimal performance of the polygenic modification score in the Fluidigm data test set. Therefore, in order to judge the explanatory power of the polygenic modification score, we combined the GWA and Fluidigm data, and evenly split the data at random 1,000 times to generate training sets and corresponding test sets. Polygenic modification scores were then based on SNPs that passed pre-specified p-value thresholds in the training data: 0.05, 0.01, 0.001, 0.0001, and 0.00001. As summarized in Figure 2, the polygenic modification score became more significant and predictive as more SNPs were used to calculate individual polygenic modification score in the test samples. The top SNP alone explained approximately 1.3% of variance in residual age at onset (Figure 2). However, the polygenic modification score, representing the genetic predisposition to deviate from the expected age at onset for a given CAG repeat size, was yet more predictive. Polygenic modification scores based on SNPs with p-values smaller than 0.05, 0.01, 0.001, 0.0001, and 0.00001 in the training samples (Figure S7), explained approximately 5.3, 3.9, 2.8, 2.4, and 2.3% of the variance in residual age at onset of the test samples, respectively. The substantially increased R-squared values by polygenic modification score support the notion that HD onset can be modified by many genes with small effect sizes, even though the SNPs tagging those genes are not by themselves genome-wide significant in the current data sets. To evaluate the total amount of variance in residual age at onset explained by all SNPs collectively, we performed GCTA analysis using all QC-passed SNPs in the GWA data. The SNPs collectively explained approximately 20% of the variance in residual age at onset. Notably, 18% of the variance is due to SNPs other than those in the top chromosome 15 region, as revealed by exclusion of the chromosome 15 modifier signals from the analysis. The reported GWA analysis therefore did not have sufficient power to discover all of the genetic

variation that modifies HD onset, arguing for continuation of this strategy with the largest achievable sample size.

Discussion

In summary, with candidate genotyping of HD individuals we have confirmed HD modifier loci on chromosomes 8 and 15 and identified the *MLH1* region of chromosome 3 as an additional genome-wide significant modifier locus, while polygenic modification score analyses suggest that increasing the sample size of the GWA could identify yet more loci. The chromosome 3 modifier locus highlights *MLH1*, involved in brain tissue CAG instability in *Htt* knock-in mice (14), consistent with the hypothesis that a functional impact of genetic variation in the modifier haplotype, via effects on CAG instability in the brains of HD patients, may alter CAG repeat size and thereby affect the rate of the disease process (13). This hypothesis is supported by the results of our GWA pathways analysis, which highlighted biological processes related to DNA maintenance (11). The functional variation within the modifier haplotype is associated with a delay in age at onset of 0.7 years, possibly consistent with an *MLH1* hypomorphic variant that reduces somatic expansion of the CAG repeat due to reduced MLH1 activity. In any event, the impact of the functional variation on *MLH1* is likely to be subtle, as complete loss of function of the allele would be expected to predispose to Lynch Syndrome. The correspondence between GWA significance and eQTL results for SNPs across the region also raises the possibility that a potential regulatory effect on *LRRFIP2* also contributes, either directly or indirectly via a coincident effect on *MLH1*, to the observed delay in onset. Clearly additional genetic and molecular analyses will be required to test the effects of the modifier haplotype and the mechanism by which it delays the rate of HD pathogenesis. Finally, our finding that a substantial amount of variation in HD age at

onset can be accounted for by genetic modification suggests that expanded GWA analysis with more subjects and therefore greater power could reveal additional modifier loci and biological networks of genes that offer *bona fide* therapeutic targets, validated in humans that influence the HD disease process.

Materials and Methods

Genotyping and quality control analysis

Selection of SNPs based on the recently completed GWA analysis (11) involved choosing the most significant SNPs amenable to genotyping on the Fluidigm platform for each of the top 61 independent modifier signals. Genotyping of 67 SNPs, representing 61 independent signals, was performed by the Genomics Platform at the Broad Institute on an independent HD cohort of 3,314 HD subjects from the European Huntington's Disease Network Registry Study. All SNPs had genotyping call rate greater than 90% and Hardy-Weinberg equilibrium p-value greater than 0.01. Non-independent SNPs with lower call rates were excluded from the polygenic modification score analysis. The study was approved by the Institutional Review Board of Partners HealthCare and all subjects provided informed consent for participation in HD research.

Residual age at motor diagnosis as a phenotype for association analysis

Age at onset of motor signs was based on rater estimation where available (1,443 subjects). In the absence of a rater estimate, we used age at onset data provided by family members (63 subjects) or patients (1,808 subjects). Predicted onset age was based on a phenotypic regression model describing the relationship between CAG repeat on the expanded chromosome and recorded age

at onset (6). Predicted age at onset was subtracted from observed age at onset to calculate the residual age at onset of motor signs, whose deviation from expectation represents the individual HD patient's level of modification of age at onset. For stringent replication analysis, we analyzed HD subjects with 40-55 CAG repeats with residual age at onset values within the range of the initial GWA data; since the most extreme data points have a greater potential for representing data entry or transcription errors, we excluded 5 subjects with extreme onset residuals beyond the range seen in the original GWA (Figure S1).

Association analysis, meta-analysis, conditional analysis, and extreme dichotomous analysis

In the Fluidigm data set, residual age at onset was modeled as function of a test SNP (additive model) and sex using a linear regression model. Main effect for sex was not significant in any association models. The small number of SNPs chosen for Fluidigm typing for the replication study were not sufficiently informative to distinguish sub-populations (data not shown). However, we reasoned that the discovery data set and replication data set have similar characteristics in terms of ancestry because of most individuals were from European countries. In addition, comparison of allele frequencies of replication SNPs in discovery and replication data sets revealed highly strong positive correlation (Figure S2), suggesting overall ancestry similarities between the two data sets. Subsequently, meta-analysis was performed by combining previous GWA results (11) and the current association results using the METAL program (http://genome.sph.umich.edu/wiki/METAL_Documentation) (33). Genome-wide significance was judged by meta-analysis p-value of 5E-8. To evaluate independence of chromosome 3 SNPs, GWA data and Fluidigm data were combined to perform conditional analyses. Briefly, residual age at onset was modeled as a function of either 1) rs1799977, 2) rs116483964, and 3) rs1799977

and rs116483964 together. Fixed effect linear regression models with sex covariate were constructed for conditional analysis. In addition, for chromosome 3 SNPs, we combined GWA data and Fluidigm data to perform combined extreme dichotomous analysis in which data were sorted based on the residual age at onset phenotype, and samples with the top and bottom 20% residual age at onset values were extracted (1,478 samples in each group). Logistic regression analysis was performed using extreme dichotomous phenotype as the dependent variable, a SNP as a primary continuous independent variable and sex as a covariate.

Capture sequencing analysis

Based on GWA analysis results, we chose 7 individuals who carry two minor alleles for the Chr3 top GWA SNP (i.e., rs144287831) with residual age at onset greater than 4 years. Since conditional analysis suggested the top SNP tags a single modifier chromosome, chosen HD subjects were hypothesized to carry two copies of the modifier haplotype. Design of capture probes was based on the Agilent's SureDesign online tool (https://earray.chem.agilent.com/suredesign/). A genomic region chr3:36,832,273-37,603,667 (hg19) was chosen in the SureDesign website in order to obtain ultra-long 120-mer biotinylated RNA bait probes that cover each site in the target region 5 times. To capture the entire genomic region including repeat sequences, we implemented an iterative capture probe design method. First, we input the chr3:36,832,273-37,603,667 as one contiguous region in the SureDesign website for most stringent probe design, generating 27,364 capture probes covering 63.9% of the target region. The most stringent condition will exclude repeat sequences based on repeat annotations such as RepeatMasker (http://www.repeatmasker.org/), WindowMasker (34), and Duke Uniqueness 35 (http://genome.ucsc.edu/cgi-bin/hgTrackUi?db=hg18&g=wgEncodeMapability). Secondly, un-

captured regions (663 fragmented regions) from the previous design were fed into the program again for moderate stringent design, generating 8,794 capture probes covering 48.13% of the target region. Thirdly, remaining uncaptured regions (7,272 regions) were fed into the program for least stringent probe design, generating 14,544 probes (covering 89.79% of the target region). Lastly, remaining regions were used for probe design without any stringency (3,276 probes covering 100% of target region). Thus, repeat sequences are likely to be captured by probes designed based on no stringency. In order to focus on unique sequence but still capture the entire region, we replicated probe sets designed by most, moderate, and least stringent parameters. Target DNA capture/enrichment was based on the SureSelect method (SureSelect XT2 Target Enrichment System) (35). Briefly, each genomic DNA sample was sheared to produce smaller fragments, and indexed for multiplexing. Subsequently, pooled indexed DNA was hybridized with capture probes, and DNA-probe complexes were pulled down using magnetic streptavidin beads. Enriched multiplexed libraries were sequenced for 100 bp paired-end sequencing using Illumina HiSeq at the Broad Institute. Mean per base coverage was 174.7; 94.0% and 97.4% of the region has at least 10X and 5X coverages, respectively. Sequencing data were then analyzed using the Genome Analysis Toolkit (https://software.broadinstitute.org/gatk/). We followed the Best Practices workflow to perform quality control analysis, variant discovery, and genotype calling (36).

Comparison of HD GWA modification signals to tissue eQTL signals

To determine whether modification of HD captured by significant chromosome 3 SNPs might be mediated by differential expression levels of genes in the region, we compared GWA association signals to HaploReg, GTEx eQTL data, and BRAINEAC exon level eQTL data. Initially, we counted the number of tissues in which a test SNP and a test gene were significantly associated

using HaploReg web resources, which annotated GTEx and other eQTL data sets. Due to potential tissue-specific regulation of gene expression, directions of eQTLs were not considered. Subsequently, we evaluated the patterns of correlation between modifier GWA significances and the number of significant tissues for each corresponding SNP. Next, we analyzed GTEx data focusing on brain regions and two candidate genes, *MLH1* and *LRRFIP2*. Cortex, caudate, putamen and cerebellum in GTEx data were analyzed to evaluate correspondence between tissue-specific *cis* eQTL signals and HD modification signals. Focusing on *MLH1* and *LRRFIP2* in putamen, exon array expression data from BRAINEAC were analyzed to test eQTL association with SNPs in the region, and subsequently eQTL signals were compared to HD GWA modifier association signals. Mapping of SNPs in eQTL data and HD GWA data was based on genomic coordinates (hg19 assembly).

Polygenic modification score analysis

In order to determine the explanatory power of a polygenic modification score in explaining the individual deviation from the expected age at onset for a given CAG size, we 1) obtained effect sizes and significances of SNPs from the initial GWA analysis (11), 2) calculated a modification score for the individual test sample (Fluidigm data) by summing the products of test SNP allele counts and corresponding effect sizes (http://zzz.bwh.harvard.edu/plink/profile.shtml), and 3) performed linear regression analysis by modeling residual age at onset of the test samples as a function of the polygenic modification score. The same procedure was applied for polygenic modification score analysis using Fluidigm data as a training set and GWA data as a test set. Only independent SNPs were used in this analysis. When SNPs were not independent (based on conditional analysis in the initial GWA data), the SNP with the highest genotyping call rate in the

Fluidigm data was chosen to represent the association signal in the region; 61 independent SNPs were used to drive polygenic modification scores of test samples. Chromosome 3p22.2 was represented by rs1799977. Among the 61 independent SNPs, all of which were associated (p-value < 0.05) with residual age at onset in the GWA data, 7 were associated (nominal p-value < 0.05) in the Fluidigm data. Missing genotypes in the Fluidigm test samples were ignored. Additionally, we also performed polygenic modification score analysis based on imputed Fluidigm test data by assigning expected genotypes based on allele frequency in the Fluidigm data. For a given missing SNP site in an individual, expected genotype in the dosage format was calculated by multiplying allele frequency of that SNP in the replication data set by 2 as described in the PLINK program manual (http://zzz.bwh.harvard.edu/plink/profile.shtml). The polygenic modification score was then calculated for each individual in the test samples to be used as a predictor variable of a linear regression model to explain residual age at onset of test samples. Polygenic modification score was defined as the mean of effect size of a minor allele X minor allele count based on non-missing SNPs.

Polygenic modification score analysis based on randomly chosen training and test samples from the combined data

Our Fluidigm validation data set had missing data. Missing data in the test samples may reduce the accuracy of polygenic modification score when ignored or expected genotypes were assigned. To objectively evaluate the power of polygenic modification score, we 1) combined the GWA data and Fluidigm data, 2) randomly and evenly split into training samples (3,698 samples) and test samples (3,698 samples), 3) performed association analysis using genotype and residual age at onset of training samples, 4) calculated polygenic modification score of test samples based on

effect size estimation from the training sample analysis and allele count of test samples, and 5) evaluated the significance of the polygenic modification score in explaining residual age at onset of test samples. This procedure was repeated 1,000 times to obtain unbiased estimations. Missing genotype data in the test samples were excluded from calculating the polygenic modification score. Scoring SNPs were based on association p-value of 0.05, 0.01, 0.001, 0.0001, and 0.00001 in the training samples. All SNPs were used as scoring SNPs as long as they passed the pre-specified significance thresholds.

GCTA analysis

The overall genetic contribution to residual age at onset was calculated by the GCTA (Genome-wide Complex Trait Analysis) program. Briefly, GWA data were analyzed by the restricted maximum likelihood (REML) method using the following parameters: --grm-adj, 0 and --grm-cutoff, 0.025. For standard GCTA analysis, all QC-passed SNPs in the GWA data were analyzed. The chromosome 15:31,105,000-31,315,000 region harbors two independent genome-wide significant modification signals (11). Therefore, this region was excluded from the GWA data to estimate the contribution of the chromosome 15 region to modification of age at onset.

Genomic coordinates

GRCh37/hg19 was used.

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Conflict of Interest Statement

None of the authors declares a conflict of interest

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Figure Legends

Figure 1. Summary of meta-analysis for the chromosome 3 locus.

A. GWA analysis results are shown as open grey circles, except the top SNPs shown as black circles. For two of the latter, Fluidigm genotyping data was generated on an independent study sample and subsequent meta-analysis revealed genome-wide significance for both SNPs (filled red circles). Arrows show the levels of improvement by addition of Fluidigm data. X-axis and Y-axis denote genomic coordinates (hg19 assembly) and significance of association, respectively. A line in cyan represents the recombination rate based on HapMap data (secondary Y-axis). A red dashed horizontal line marks the level of genome-wide significance, and a blue horizontal line indicates the region that was analyzed by capture sequencing analysis. All exons of transcripts (RefSeq) representing the same gene were combined to represent each gene in this region. Genes in red and blue denote genes on plus and minus strand, respectively. A red horizontal bar indicates a region expanded in panel B.

B. Expanded region denoted by the red horizontal bar in Panel A. Filled black circles, filled grey circles, and open grey circles represent SNPs with allele frequencies between 31 and 32%, higher than 32%, and below 31%, respectively. IDs of SNPs with minor allele frequency between 31 and 32% are shown. This region harbors exons of various transcripts from the 3' portion of *MLH1* (red) and the 5' portion of *LRRFIP2* (blue). Representative transcripts with different exons in this region were obtained from RefSeq and UCSC Genome Browser.

Figure 2. Increased explanatory power of the polygenic modification score.

Combined data were randomly split into a training and test set of equal size to perform polygenic modification score analysis. For a given split, polygenic modification score in the test samples was calculated based on independent SNPs with training set p-value smaller than 0.05 (purple), 0.01 (red), 0.001 (green), 0.0001 (blue) or 0.00001 (orange). Then, linear regression analysis was performed by modeling residual age at onset of test samples as a function of polygenic modification scores based on multiple SNPs with different levels of training set association analysis p-value. For each iteration, we recorded p-value and R-square value of the polygenic modification score. The main plot in the center shows significance (Y-axis) and percent R-squared values of polygenic modification score. Histograms on the top and on the right side of the main plot show the distributions of R-squared and significance values, respectively. As a reference, significance and R-squared value of the model based on the single most significant SNP are shown in grey.

Table 1. Single SNP association analysis and meta-analysis significance of candidate SNPs with modification of HD*

SNP	Chr	BP (hg19)	Reference allele	Alternative (test) allele)	GWA data (n = 4,082)			Replication data (n = 3,314)			Meta-analysis p-value	Gene [$]
					MAF	Beta	p-value	MAF	Beta	p-value		
rs34852161	8	103,284,508	C	A	0.083	-1.48	3.43E-07	0.084	-0.87	0.00737	2.39E-08	*UBR5*
rs150393409	15	31,202,961	G	A	0.016	-5.54	9.34E-18	0.013	-2.38	0.00307	5.95E-17	*FAN1*
rs35811129	15	31,241,346	G	A	0.272	1.37	1.16E-13	0.265	1.29	2.0E-10	1.55E-22	*MTMR10*
rs1799977	3	37,053,568	A	G	0.319	0.89	7.16E-07	0.305	0.59	0.00258	1.19E-08	*MLH1*
rs116483964	3	37,102,696	G	A	0.320	0.92	4.02E-07	0.303	0.58	0.0031	8.84E-09	*MLH1/ LRRFIP2*

* Results of linear regression analysis of candidate SNPs using GWA data and replication data are summarized. For both SNPs, alternative alleles (test alleles) are minor alleles in our data. Chr, MAF, and beta represent chromosome, minor allele frequency, and slope estimation, respectively.

[$] Genes represent nearest genes, not necessarily causal modifier genes.

Table 2. Extreme dichotomous analysis and conditional analysis of chromosome 3 SNPs*

A. Dichotomous analysis	
Test SNP	p-value
rs1799977	5.3E-09
rs116483964	5.6E-09

B. Conditional analysis	
Test SNP	p-value
rs1799977	9.5E-09
rs116483964	6.2E-09
rs1799977 conditioned by rs116483964	0.9818
rs116483964 conditioned by rs1799977	0.5145

* For dichotomous analysis, extreme late and extreme early groups (1,478 samples for each group) comprising top and bottom 20% of subject based on samples sorted by residual age at onset in a descending order were identified from combined data set (GWA data + Fluidigm data). Then, logistic regression analysis was performed for each SNP using the test SNP as the main predictor variable and sex as a covariate. For conditional analysis, GWA data and Fluidigm data were combined to perform fixed effect model linear regression analysis to determine independence of the two SNPs. Two SNPs were used simultaneously as independent variables in a linear regression model, and corresponding p-values are obtained. For extreme dichotomous phenotype analysis, 2 subsets of data were extracted from the combined data set based on residual age at onset phenotype.

Table 3. Modifier haplotype defined by top-scoring SNPs*

SNP	Chr 3 bp (hg19)	minor allele	major allele	MAF All samples	MAF 1st AO residual quartile	MAF 2nd AO residual quartile	MAF 3rd AO residual quartile	MAF 4th AO residual quartile	P-value quantitative analysis of AO residual	P-value dichotomous analysis of AO residual 20% extremes
rs1799977	37,053,568	G	A	0.319	0.279	0.298	0.324	0.351	7.2E-07	2.7E-06
rs144287831	37,068,079	C	T	0.312	0.279	0.297	0.322	0.350	2.2E-07	1.5E-06
rs141716664	37,078,200	T	-	0.315	0.281	0.299	0.323	0.350	4.4E-07/	3.5E-06
rs116483964	37,102,696	A	G	0.320	0.279	0.296	0.322	0.351	4.0E-07	2.1E-06
rs148648107	37,118,345	A	G	0.318	0.280	0.297	0.323	0.350	9.6E-07	4.3E-06
rs11714838	37,121,844	A	G	0.318	0.281	0.297	0.323	0.352	1.3E-06	5.0E-06
rs147891316	37,131,815	T	G	0.317	0.280	0.297	0.323	0.351	1.1E-06	7.8E-06

*Allele frequencies of SNPs in GWA data were analyzed to localize functional variation. Subjects in GWA analysis were grouped into quartile bins based on their residual age at onset; 1st and 4th AO residual quartiles represent earliest and latest age at onset groups, respectively. Then, minor allele frequencies of SNPs were calculated for each quartile bin to understand how alleles are distributed relative to residual age at onset phenotype. MAF means minor allele frequency. P-value quantitative analysis of AO residual represents the p-value in the original GWA analysis. P-value dichotomous analysis of AO residual 20% extremes represent p-values from the logistic analysis of GWA data.

Abbreviations”

Chr: chromosome

EHDN: European Huntington’s Disease Network

eQTL: expression Quantitative Trait Locus

GCTA: Genome-wide Complex Trait Analysis

GWA: Genome-wide Association

HD: Huntington’s Disease

MAF: minor allele frequency

QC: quality control

SNP: single nucleotide polymorphism

Supplemental Tables

Table S1 - Genotype of replication samples
See excel file TableS1.xls

Table S2. SNPs analyzed in replication samples and for polygenic modification score
See excel file TableS2.xls

Table S3. Consensus alleles of the effect haplotype. *

SNP ID	Chromosome	BP (hg19)	Reference allele	Alternative allele	Consensus allele	Number of consensus allele
rs4647224	3	37,043,230	G	A	A	14
rs59335282	3	37,043,443	GT	G	G	14
rs28393182	3	37,043,459	T	G	G	14
rs3774341	3	37,045,233	A	C	C	14
rs9871903	3	37,047,433	G	A	A	14
rs113479434	3	37,047,777	G	A	A	14
rs4234259	3	37,048,633	A	G	G	14
rs4647250	3	37,049,098	T	C	C	14
rs113956733	3	37,052,070	T	C	C	14
rs1799977	3	37,053,568	A	G	G	14
rs4647260	3	37,054,601	T	C	C	14
rs1558528	3	37,056,990	C	A	A	14
rs4647269	3	37,057,591	C	T	T	14
rs4647277	3	37,058,509	A	G	G	14
rs11710807	3	37,060,321	C	T	T	14
rs141017393	3	37,060,733	G	A	G	13
rs2286939	3	37,062,040	T	C	C	14
rs3774339	3	37,062,854	C	T	T	14
rs3774338	3	37,062,959	G	T	T	14
rs28754348	3	37,063,728	G	A	A	14
rs186532057	3	37,065,425	G	A	G	13
rs6550445	3	37,066,369	T	C	C	14
rs6550446	3	37,066,373	T	A	A	14
rs11129748	3	37,067,050	A	G	G	14
rs144287831	3	37,068,079	T	C	C	14
rs6781146	3	37,068,257	C	T	T	14

rs143397020	3	37,068,331	GAATAATAAT	G	G	14
rs9852810	3	37,068,969	G	A	A	14
rs11719992	3	37,069,872	T	G	G	14
rs2286940	3	37,070,106	C	T	T	14
rs3774335	3	37,072,627	A	C	C	14
rs3774334	3	37,072,705	G	A	A	14
rs9819025	3	37,073,287	T	G	G	14
rs6765395	3	37,073,579	T	G	G	14
rs3821826	3	37,074,368	C	G	G	14
rs997588	3	37,075,142	G	A	A	13
rs6772548	3	37,075,934	T	C	C	14
rs6784088	3	37,075,984	A	G	G	14
rs6550447	3	37,078,280	G	C	C	14
rs4678925	3	37,078,506	A	G	G	14
rs748766	3	37,082,874	T	C	C	14
rs9876116	3	37,083,740	A	G	G	14
rs67401825	3	37,085,970	T	C	C	14
rs9822082	3	37,086,204	G	A	A	14
rs75839046	3	37,086,416	A	G	A	12
rs184308009	3	37,087,179	T	C	T	12
rs9831178	3	37,087,417	C	T	T	14
rs11926842	3	37,088,102	A	T	T	14
rs11290150	3	37,089,840	CT	C	C	14
rs2241031	3	37,090,274	C	T	T	14
rs1860968	3	37,091,325	G	A	A	14
rs1558529	3	37,093,064	T	C	C	14
rs4579	3	37,094,679	G	A	A	14
rs10849	3	37,095,070	C	T	T	14
rs4678932	3	37,096,303	T	G	G	14
rs2110194	3	37,097,087	C	T	T	14

rs2363499	3	37,097,546	A	G	G	14
rs202119305	3	37,097,949	CT	C	C	14
rs143498278	3	37,098,064	C	T	C	10
rs58257408	3	37,099,025	CT	C	C	14
rs3774327	3	37,099,367	G	A	A	14
rs3774326	3	37,099,566	G	A	A	14
rs7639327	3	37,099,788	A	G	G	14
rs202036094	3	37,100,166	CAAA	C	C	14
rs7372653	3	37,101,079	G	A	A	14
rs11720064	3	37,101,519	G	T	T	14
rs139922612	3	37,102,458	AGTGC	A	A	14
rs58693636	3	37,102,623	C	T	T	14
rs116483964	3	37,102,696	G	A	A	14
rs145261675	3	37,102,874	CTTTTCT	C	C	14
rs6808735	3	37,104,246	A	C	C	14
rs2058476	3	37,104,896	G	T	T	14
rs1468712	3	37,106,013	T	C	C	14
rs1468713	3	37,106,115	A	G	G	14
rs7639375	3	37,107,022	C	A	A	14
rs2302503	3	37,107,470	G	A	A	14
rs6550448	3	37,108,896	T	A	A	14
rs56180213	3	37,109,633	C	A	A	14
rs9823428	3	37,111,130	G	A	A	14
rs17810211	3	37,113,405	T	C	C	14
rs3836485	3	37,115,313	GC	G	G	14
rs1558527	3	37,115,658	T	C	C	14
rs7651033	3	37,116,042	C	T	T	14
rs2302504	3	37,116,386	G	T	T	14
rs11709376	3	37,116,808	C	G	G	14
rs726769	3	37,117,741	A	G	G	14

rs148648107	3	37,118,345	G	A	A	14
rs4678935	3	37,119,835	A	C	C	14
rs9810355	3	37,121,074	A	G	G	14
rs6806487	3	37,121,092	C	T	T	14
rs6806861	3	37,121,293	G	A	A	14
rs9814918	3	37,121,613	A	G	G	14
rs11707197	3	37,122,329	A	C	C	14
rs6550449	3	37,122,997	A	G	G	14
rs6550450	3	37,123,099	C	G	G	14
rs6550451	3	37,123,250	G	A	A	14
rs1990492	3	37,124,620	A	G	G	14
rs9846039	3	37,125,699	C	T	T	14
rs113687377	3	37,127,076	CT	C	C	14
rs3821824	3	37,130,942	G	C	C	14
rs2302505	3	37,131,404	C	T	T	14
rs147891316	3	37,131,815	G	T	T	14
rs9879135	3	37,132,279	G	A	A	14
rs113267946	3	37,132,719	GA	G	G	14
rs2302506	3	37,133,124	A	G	G	14
rs11915301	3	37,133,853	G	A	A	14
rs3774323	3	37,134,451	T	C	C	14
rs17204675	3	37,135,797	T	C	C	14
rs9820888	3	37,136,711	T	G	G	14
rs67385735	3	37,138,751	A	G	G	14
rs5847949	3	37,139,597	AT	A	A	14
rs7638252	3	37,141,732	G	C	C	14
rs57588408	3	37,141,928	CAT	C	C	14
rs7616160	3	37,141,977	A	G	G	14
rs143418804	3	37,142,394	T	C	T	13
rs571725354	3	37,064,415	G	A	G	13

rs554553185	3	37,100,477	A	G	A	13
rs527583094	3	37,126,407	T	C	T	13

* Seven HD individuals who carry two minor alleles for rs144287831 were captured to determine the sequence of Chr3:36 ,832,347-37,603,667 region. Variable sites and alternative alleles in 7 individuals were detected in the capture sequencing data, and consensus alleles among 14 chromosomes in this region were identified by taking the most frequent alleles for each site. Therefore, consensus alleles in this table represent either 1) reference or alternative alleles predominant in 14 chromosomes, or 2) alternative alleles present on all 14 chromosomes. For each site, the number of defined consensus allele s was counted among 14 chromosomes. For example, 14 means all 14 chromosomes carry the consensus allele for a given site.

Table S4. Polygenic modification score analysis. *

Analysis	Training set	Test set	Score SNPs	Handling of missing genotype in the test set	P-value
A	GWA	Fluidigm	p-value < 0.05 in the training set	Excluded	0.0157
B	Fluidigm	GWA	(61 independent SNPs)	No missing data in the test set	4.0E-26
C	GWA	Fluidigm	p-value < 0.05 in the training set	Expected genotype was assigned based on allele frequency	0.0144

***** Using 61 independent SNPs typed in the Fluidigm data, we performed polygenic modification score analysis.

A) GWA data were analyzed to estimate effect size of SNPs and to calculate p-values. Subsequently, the polygenic modification score of Fluidigm data based on SNPs with GWA analysis p-value smaller than 0.05 was calculated. Then, residual age at onset of Fluidigm samples was modeled as a function of polygenic modification score in a linear regression model to determine its explanatory power.

B) The same procedures were performed using Fluidigm data as a training set and GWA data as a test set.

C) The same SNPs as in analysis A were used to calculate the polygenic modification score of Fluidigm data imputed for missing genotype. For a missing site in a given individual, allele frequency of the minor allele multiplied by 2 was used as an expected genotype to calculate the polygenic modification score. The same analytical pipeline was used to determine the significance of the polygenic modification score.

Supplemental Figures

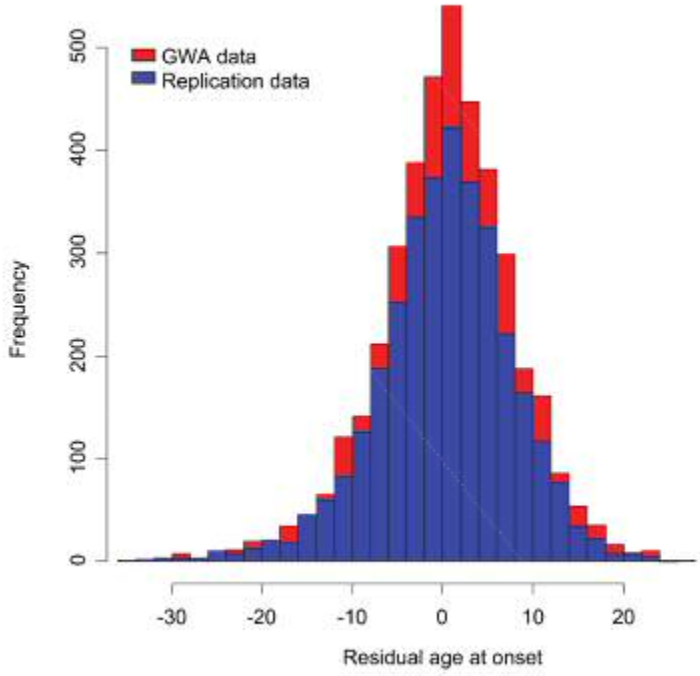

Figure S1. Residual age at onset phenotype of replication data.

Distribution of residual age at onset of replication samples (histogram in blue) was compared to that of GWA data (histogram in red) to visually confirm the homogeneity of phenotypes of replication samples and GWA samples.

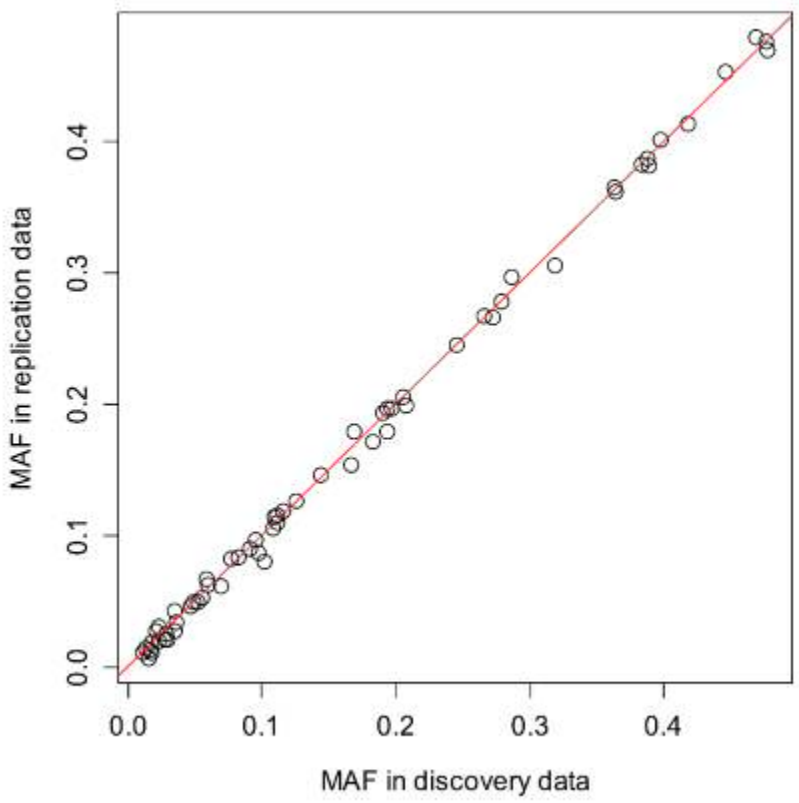

Figure S2. Minor allele frequencies of test SNPs in the discovery and replication data sets

For 61 SNPs we focused on for the replication analysis, minor allele frequencies in discovery set (GWA data; X-axis) and replication set (Fluidigm data; Y-axis) are compared.

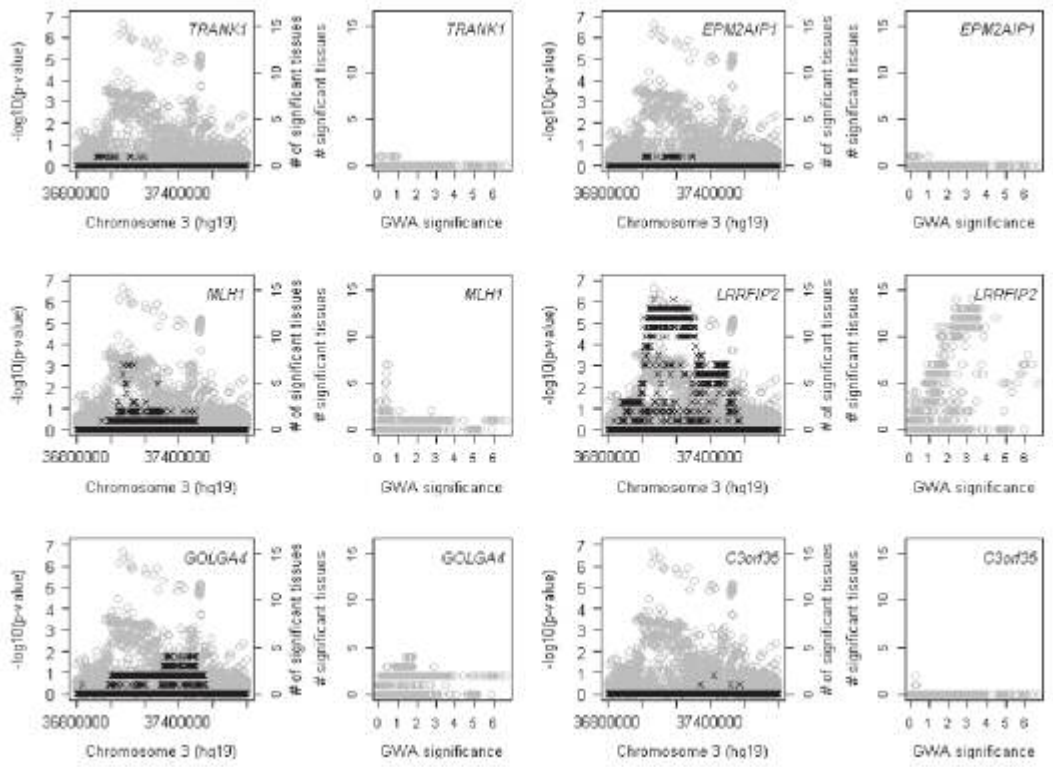

Figure S3. Correspondence between GWA modification signals and *cis* eQTL signals.

To explore the molecular mechanisms of modification conferred by the chromosome 3 locus, we determined whether GWA modifier association signals were similar to eQTL signals in tissues. For a given gene, we counted the number of significant tissues associated with SNPs in the HaploReg annotation data base regardless of the effect sizes. Each gene was graphed using two plots. The plot on the left shows GWA association signal on the primary Y-axis (grey circles) and the number of tissues with significant eQTLs on the secondary Y-axis (black crosses) for all SNPs. For shared SNPs between our GWA data and HaploReg data base, significance (-log10p-value) in GWA data (X-axis) were directly compared to the number of significant tissues (plot on the right).

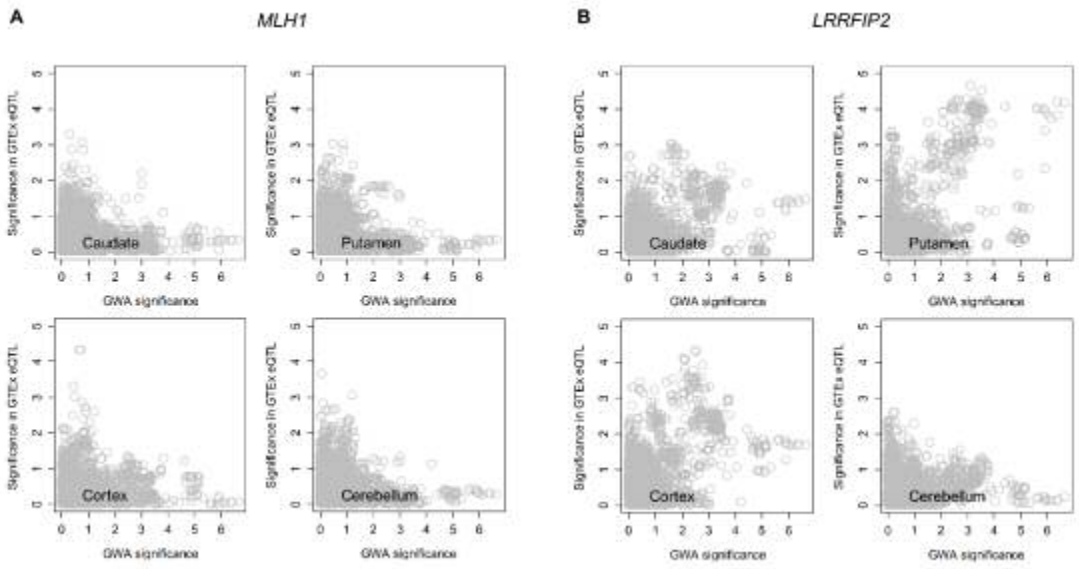

Figure S 4. SNPs associated with expression levels of *MLH1* and *LRRFIP2* in brain sub-regions.

MLH1 and *LRRFIP2* showed promising correspondence with *cis* eQTL signals. Subsequently, we evaluated the brain eQTL signals in GTEx data, and compared to our GWA modifier signals. Caudate (top left), putamen (top right), cortex (bottom left), and cerebellum (bottom right) were analyzed for eQTL data in GTEx data (version 6). Significance of SNPs is represented by -log10(p-value) on both axes.

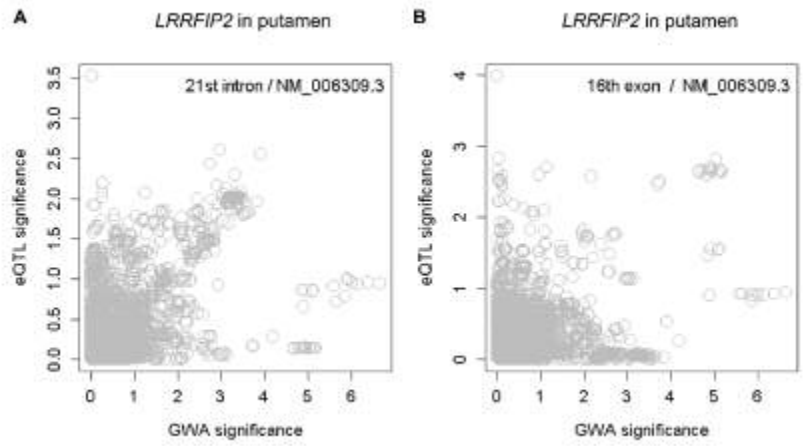

Figure S 5. Relationship between *cis* eQTL signals for *LRRFIP2* in putamen and GWA modification association signals in BRAINEAC data.

BRAINEAC data (http://www.braineac.org/) was analyzed to further evaluate the impacts of SNPs on mRNA expression levels of *MLH1* and *LRRFIP2* in putamen. 129 putamen samples were analyzed in BRAINEAC. Expression levels of each region determined by BRAINEAC were modeled as a function of SNP in a linear regression analysis framework. Then, significances (i.e., -log10(p-value) from eQTL analysis (Y-axis) were compared to significances from HD onset modifier GWA analysis (X-axis; -log10(p-valud)). Most of exons of *MLH1* or *LRRFIP2* did not show trends of correlation between eQTL signals and GWA modifier association signals. However, eQTL signals for chr3:37 ,108,538-37,110,067 (A; 21st intron of *LRRFIP2*, NM_006309.3) and chr3:37 ,138,107-37,138,136 (B; 16th exon of *LRRFIP2*, NM_006309.3) in putamen weakly corresponded with modifier association signals.

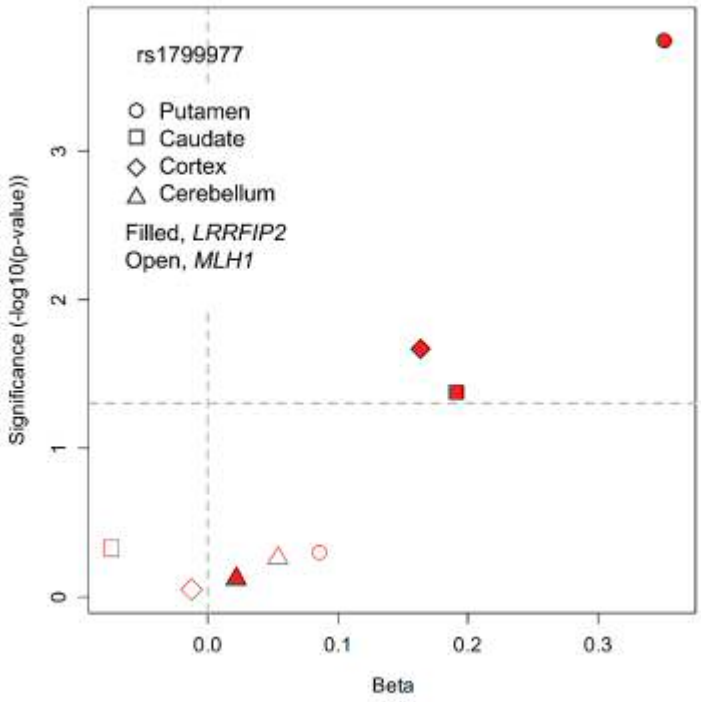

Figure S6. Association of rs116483964 and rs1799977 with the expression levels of *MLH1* and *LRRFIP2* in brain regions. Expression levels of *MLH1* (open symbols) and *LRRFIP2* (filled symbols) in putamen (circle), caudate (square), cortex (diamond), and cerebellum (triangle) were compared against rs1799977 in the GTEx data. The levels of *cis* eQTL significance of each SNP-gene pair in a given brain region (Y-axis) were plotted against corresponding normalized effect sizes (i.e., beta on X-axis). A vertical and a horizontal grey dashed line, respectively represent a slope of zero and nominal significance of 0.05.

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Table S1. Genotype of replication samples.

ID	Residual age at onset	rs113605276	rs1146382	rs115068682	rs45576236	rs3820400	rs10159075	rs75376497
fluidigm.1	0.4320	C C	C T	C T	A A	A G	A G	G G
fluidigm.2	3.3616	C C	C T	T T	A G	A G	A A	G G
fluidigm.3	-9.7580	C C	T T	T T	A A	G G	A A	G G
fluidigm.4	16.2420	C C	C T	T T	A A	A G	A G	G G
fluidigm.5	1.6159	C C	C T	T T	A G	A G	A G	G G
fluidigm.6	10.1557	C C	C T	T T	A A	A G	A A	G G
fluidigm.7	2.2804	C C	C T	T T	A A	A G	A A	C G
fluidigm.8	14.0958	C C	C T	C T	A A	G G	A A	G G
fluidigm.9	16.3177	C C	T T	T T	A G	G G	A A	G G
fluidigm.10	-10.6384	C C	C T	T T	A G	G G	A A	G G
fluidigm.11	0.0847	C T	T T	T T	A A	G G	A G	G G
fluidigm.12	2.6159	C C	T T	T T	A A	G G	A A	G G
fluidigm.13	5.0847	C C	C T	T T	A G	A G	A A	C G
fluidigm.14	0.6159	C C	T T	T T	A A	A A	A A	G G
fluidigm.15	7.2804	C C	T T	T T	A A	G G	A G	G G
fluidigm.16	-6.6823	C C	C T	C T	A A	A G	A A	G G
fluidigm.17	1.8897	C C	C C	T T	A G	G G	A A	G G
fluidigm.18	1.3616	C C	C C	T T	A A	A G	A A	G G
fluidigm.19	-0.7196	C C	C T	T T	A G	A G	A A	G G
fluidigm.20	5.8345	C C	T T	T T	A A	A G	A A	G G
fluidigm.21	4.1885	C C	C C	T T	A A	A G	A A	G G
fluidigm.22	-7.8115	C C	C T	T T	A A	G G	A A	G G
fluidigm.23	6.4320	C C	T T	T T	A G	A G	A G	C G
fluidigm.24	-3.3841	C C	C T	T T	A A	A G	A A	C G
fluidigm.25	6.2420	C C	T T	T T	A A	A G	A G	G G
fluidigm.26	6.2420	C T	T T	T T	A A	A A	A A	G G
fluidigm.27	-1.6384	C C	C T	T T	A A	G G	A A	G G
fluidigm.28	-0.3841	C C	T T	T T	A A	A A	A A	G G
fluidigm.29	14.2804	C C	C T	C T	A A	G G	A A	G G
fluidigm.30	-3.1103	C C	T T	T T	A G	G G	A A	G G
fluidigm.31	11.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.32	12.3177	C C	C T	T T	A A	G G	A A	G G
fluidigm.33	-21.6823	C C	C T	T T	A A	A G	A A	G G
fluidigm.34	-16.1103	C C	T T	T T	A G	A G	A G	G G
fluidigm.35	-2.5680	C C	C T	C T	A A	A A	A A	G G
fluidigm.36	-5.6823	C C	T T	T T	A A	G G	A A	G G
fluidigm.37	8.8897	C C	C T	T T	A A	A G	A A	G G
fluidigm.38	-2.0313	C C	C T	C T	A G	A A	A A	G G
fluidigm.39	-4.9042	C C	T T	T T	G G	G G	A G	C G
fluidigm.40	-6.1103	C C	C C	T T	A G	G G	A A	G G

fluidigm.41	-3.6823	C C	C T	T T	A G	A A	A A	G G
fluidigm.42	9.3177	C C	C T	T T	A G	G G	A A	G G
fluidigm.43	14.3177	C T	C C	C T	A A	A G	A G	G G
fluidigm.44	6.1557	C C	C T	T T	G G	A G	A A	G G
fluidigm.45	5.8897	C C	T T	T T	A A	A G	A G	G G
fluidigm.46	-7.7580	C C	C T	T T	A A	A G	A G	G G
fluidigm.47	4.8897	C C	C T	T T	A G	G G	A G	G G
fluidigm.48	-5.1103	C C	C C	T T	A G	A G	A A	G G
fluidigm.49	4.0958	C T	C C	C T	A A	G G	A A	G G
fluidigm.50	-8.6384	C C	C T	T T	A A	G G	A A	G G
fluidigm.51	-5.6384	C C	C C	T T	A A	G G	A A	G G
fluidigm.52	-2.7196	C C	T T	C T	A A	A G	A A	G G
fluidigm.53	-13.7580	C C	C C	T T	A A	G G	A A	G G
fluidigm.54	6.8897	C C	T T	T T	A G	G G	A A	G G
fluidigm.55	-3.7196	C C	C C	T T	A A	A G	A G	G G
fluidigm.56	-1.6823	C C	C T	T T	A G	A A	A A	G G
fluidigm.57	7.4671	C C	C T	T T	A A	A A	A A	G G
fluidigm.58	7.3177	C C	C T	T T	A A	A G	A A	G G
fluidigm.59	2.2420	C T	C T	T T	A A	A G	A A	G G
fluidigm.60	-1.7196	C C	T T	T T	A A	G G	A A	G G
fluidigm.61	-7.7580	C C	T T	T T	A A	A G	A A	C G
fluidigm.62	-7.7196	C T	C T	T T	A G	A G	A A	G G
fluidigm.63	-1.9153	C C	T T	T T	A A	A G	A G	G G
fluidigm.64	1.4671	C C	C T	T T	A A	G G	A A	G G
fluidigm.65	-0.5680	C C	C C	T T	A A	G G	A A	G G
fluidigm.66	-4.7580	C C	T T	T T	A A	G G	A A	G G
fluidigm.67	1.2804	C C	T T	T T	A G	G G	A A	G G
fluidigm.68	0.2804	C C	C C	T T	A A	A A	A A	G G
fluidigm.69	-4.1103	C C	T T	T T	A A	A G	A A	G G
fluidigm.70	1.2420	C C	T T	T T	A A	G G	A A	G G
fluidigm.71	6.4320	C C	T T	T T	A A	A G	A A	G G
fluidigm.72	0.3616	C C	C T	T T	G G	A G	A A	G G
fluidigm.73	-1.9153	C C	T T	T T	A A	A A	A A	G G
fluidigm.74	-8.5680	C C	C T	T T	A G	A G	A A	G G
fluidigm.75	5.2420	C C	T T	T T	A G	G G	A G	G G
fluidigm.76	2.8897	C C	C C	T T	A A	A G	A A	G G
fluidigm.77	2.4320	C C	T T	T T	A A	G G	A A	G G
fluidigm.78	-2.7580	C C	C T	C T	A G	A G	A A	G G
fluidigm.79	0.8897	C C	C T	T T	A G	G G	A A	G G
fluidigm.80	-1.5680	C C	C T	T T	A A	A A	A A	G G
fluidigm.81	-2.3841	C C	C T	T T	A A	G G	A A	C G
fluidigm.82	3.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.83	4.0847	C C	T T	T T	A A	A G	A A	G G

fluidigm.84	6.0958	C C	C T	T T	A G	A G	A A	C G
fluidigm.85	2.3177	C C	C C	T T	A A	A G	A A	G G
fluidigm.86	1.3177	C T	C T	T T	A A	A A	A A	G G
fluidigm.87	6.4320	C C	C C	T T	A A	G G	A A	G G
fluidigm.88	3.0958	C T	C T	T T	A A	G G	A A	G G
fluidigm.89	-7.6823	C C	C T	T T	A A	G G	A A	G G
fluidigm.90	0.0958	C C	T T	T T	A A	G G	A A	G G
fluidigm.91	-3.7580	C C	C T	T T	G G	G G	A G	G G
fluidigm.92	6.0958	C T	T T	T T	A G	A G	A A	G G
fluidigm.93	-17.7580	C C	C C	T T	G G	G G	A A	G G
fluidigm.94	-2.5680	C C	T T	T T	A A	A G	A A	G G
fluidigm.95	1.4320	C C	C T	T T	A A	A G	A A	G G
fluidigm.96	22.0958	C C	C T	T T	A A	A G	A A	G G
fluidigm.97	-4.5680	C C	C T	0 0	A G	A A	A A	G G
fluidigm.98	-0.6823	C C	C T	T T	A A	G G	A A	C G
fluidigm.99	4.4320	C C	C C	T T	A A	A G	A G	G G
fluidigm.10(	0.8897	C C	T T	T T	A A	A G	A A	G G
fluidigm.101	3.0958	C C	C T	T T	A G	G G	A A	G G
fluidigm.102	9.8897	C C	C C	T T	A G	A G	A A	G G
fluidigm.103	-12.1103	C C	C T	T T	A G	G G	A G	G G
fluidigm.104	-5.5680	C C	C T	T T	G G	A G	A A	C G
fluidigm.105	7.2420	C C	T T	T T	A A	G G	A A	G G
fluidigm.106	-19.6823	C C	C C	T T	A A	G G	A A	G G
fluidigm.107	-11.1103	C C	C T	T T	A G	G G	A G	G G
fluidigm.108	3.8897	C C	T T	T T	A A	A G	A A	G G
fluidigm.109	11.6159	C C	C C	T T	A G	G G	A G	G G
fluidigm.11(	-14.9042	C C	C T	0 0	A G	A A	A A	G G
fluidigm.111	-7.6384	C C	T T	T T	A A	G G	A A	G G
fluidigm.112	-6.7580	C C	T T	0 0	A A	G G	A A	G G
fluidigm.113	0.2420	C C	T T	T T	A A	A G	A A	G G
fluidigm.114	1.2804	C C	C C	T T	A A	A G	A A	G G
fluidigm.115	7.2420	C C	T T	T T	A A	A G	A A	G G
fluidigm.116	-0.1103	C C	C T	T T	A G	A G	A A	G G
fluidigm.117	-8.7580	C C	C T	T T	A A	G G	A A	G G
fluidigm.118	2.0958	C C	T T	T T	A A	G G	A A	G G
fluidigm.119	21.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.12(	-9.7580	C T	C C	T T	A A	A G	A A	G G
fluidigm.121	-0.3841	C C	C C	T T	A A	G G	A A	G G
fluidigm.122	5.2420	C C	C T	T T	A G	A G	A A	G G
fluidigm.123	8.2804	C C	C T	T T	A A	A G	A G	G G
fluidigm.124	-7.1103	C C	C T	0 0	A A	A A	A A	G G
fluidigm.125	-0.7196	C C	T T	T T	A A	A G	A G	G G
fluidigm.126	-0.5680	C C	T T	T T	G G	A G	A A	G G

fluidigm.127	-5.1103	C C	C T	T T	A A	A G	A A	G G
fluidigm.128	-10.9042	C C	T T	0 0	A A	A A	A A	G G
fluidigm.129	-9.9042	C C	C T	T T	A G	A A	A A	C G
fluidigm.130	-0.0313	C C	C T	0 0	A A	G G	A A	G G
fluidigm.131	-6.6823	C C	T T	T T	A A	G G	A A	G G
fluidigm.132	-4.1103	C C	C C	T T	A G	A G	A A	C G
fluidigm.133	-3.6823	C C	C T	0 0	A G	A G	A A	G G
fluidigm.134	-21.1103	C C	T T	T T	A G	G G	A A	C G
fluidigm.135	2.2420	C C	T T	T T	A A	G G	A A	G G
fluidigm.136	-6.9042	C C	C T	T T	A A	A A	A A	G G
fluidigm.137	-10.6823	C T	C T	T T	A A	A G	A G	C G
fluidigm.138	-1.3841	C C	T T	T T	A G	G G	A A	C G
fluidigm.139	5.4320	C C	T T	T T	A A	A G	A A	G G
fluidigm.140	1.9687	C C	T T	T T	A G	A G	A A	G G
fluidigm.141	4.8897	C C	T T	T T	A A	A A	A A	C G
fluidigm.142	-6.5680	C C	C T	T T	A G	A A	A A	G G
fluidigm.143	-14.1103	C C	T T	T T	A A	A G	A A	G G
fluidigm.144	-12.6823	C C	C T	T T	G G	A G	A A	G G
fluidigm.145	-2.9042	C C	C C	T T	A G	G G	A A	G G
fluidigm.146	4.3177	C C	T T	T T	A A	G G	A G	G G
fluidigm.147	-0.7580	C C	C T	T T	A G	A A	A A	G G
fluidigm.148	-2.5680	C C	C C	T T	A A	A A	A A	G G
fluidigm.149	-10.7580	C C	C T	T T	A A	A G	A A	C G
fluidigm.150	4.4320	C C	C T	T T	A A	A A	A A	G G
fluidigm.151	-2.9042	C C	T T	T T	G G	G G	A A	G G
fluidigm.152	-3.9153	C C	T T	T T	A A	A G	A A	G G
fluidigm.153	9.8897	C C	C T	T T	A G	A G	A A	G G
fluidigm.154	0.0847	C C	C T	T T	A A	A A	A A	G G
fluidigm.155	-18.9042	C C	C C	T T	A A	A G	A A	G G
fluidigm.156	-0.6384	C C	T T	T T	A A	A A	A A	G G
fluidigm.157	2.1885	C C	T T	T T	A G	A A	A A	G G
fluidigm.158	-9.9042	C C	C T	C T	A G	A G	A A	G G
fluidigm.159	1.3177	C C	C T	T T	A A	G G	A A	G G
fluidigm.160	-14.7580	C C	C T	T T	A A	G G	A A	G G
fluidigm.161	-2.7196	C C	T T	T T	A G	G G	A A	G G
fluidigm.162	1.8897	C C	C C	C T	A A	A G	A G	G G
fluidigm.163	3.2420	C C	T T	T T	A A	A G	A A	G G
fluidigm.164	-4.0313	C C	C T	T T	A G	G G	A A	G G
fluidigm.165	-6.3841	C C	C T	T T	A A	G G	A G	G G
fluidigm.166	-8.9042	C C	C C	T T	A A	A G	A A	G G
fluidigm.167	1.4671	C C	C T	T T	A A	A A	A A	G G
fluidigm.168	-3.7196	C C	C C	T T	A A	A G	A A	G G
fluidigm.169	2.8897	C C	C T	T T	A A	G G	A A	G G

fluidigm.17(	-17.5680	C C	C T	T T	A G	G G	A A	G G
fluidigm.171	-5.9042	C C	T T	T T	A A	A A	A A	G G
fluidigm.172	-0.7196	C C	C C	T T	A G	A A	A A	G G
fluidigm.173	6.2420	C C	C T	T T	A A	A A	A A	G G
fluidigm.174	-12.9042	C C	C T	T T	A A	G G	A G	G G
fluidigm.175	0.8897	C C	C T	T T	A A	G G	A A	G G
fluidigm.176	14.6159	C T	T T	T T	A A	G G	A A	G G
fluidigm.177	-1.0313	C C	C T	T T	A A	G G	A G	G G
fluidigm.178	-8.1103	C C	C T	T T	A G	G G	A A	G G
fluidigm.179	12.0958	C C	T T	T T	A A	G G	A A	G G
fluidigm.180	-5.7580	C C	T T	T T	A G	G G	A A	G G
fluidigm.181	2.2420	C T	C T	T T	A A	G G	A A	G G
fluidigm.182	-4.6823	C C	C T	T T	A G	A A	A A	G G
fluidigm.183	-6.5680	C C	C T	T T	A A	A G	A A	G G
fluidigm.184	0.0847	C C	C T	T T	A A	A G	A A	G G
fluidigm.185	-2.7196	C C	C T	T T	A A	A G	A A	G G
fluidigm.186	3.9687	C C	C C	T T	A A	G G	A G	G G
fluidigm.187	-4.1103	C C	C T	T T	A A	A A	A G	G G
fluidigm.188	7.0958	C C	C T	T T	A A	A G	A A	G G
fluidigm.189	8.2420	C C	T T	T T	A G	G G	A A	G G
fluidigm.190	8.2804	C C	C T	T T	A A	G G	A A	G G
fluidigm.191	-1.7196	C C	C T	T T	A A	A G	A A	G G
fluidigm.192	-6.6823	C C	C T	T T	A G	A G	A G	G G
fluidigm.193	10.4320	C C	C T	T T	A A	A G	A A	G G
fluidigm.194	1.3616	C C	C T	T T	A G	G G	A A	G G
fluidigm.195	-7.5680	C C	C T	T T	A A	A G	A A	G G
fluidigm.196	-5.7196	C C	C T	C T	A A	A G	A A	G G
fluidigm.197	2.2804	C C	C T	T T	A A	G G	0 0	G G
fluidigm.198	-1.6384	C C	C T	T T	A A	A G	A A	C G
fluidigm.199	0.4320	C C	C T	T T	A A	G G	A A	G G
fluidigm.200	2.8897	C C	C T	T T	A A	A G	A G	G G
fluidigm.201	15.2804	C C	C T	T T	A A	A G	A A	G G
fluidigm.202	0.8897	C T	T T	T T	A G	A G	A G	G G
fluidigm.203	-2.7580	C T	T T	T T	A A	G G	A A	G G
fluidigm.204	2.1557	C C	C T	T T	A A	A G	A A	C G
fluidigm.205	-2.6823	C C	C T	T T	A A	A A	A A	G G
fluidigm.206	-2.5680	C C	C C	T T	A A	G G	A A	G G
fluidigm.207	11.8897	C C	T T	T T	A G	A A	A G	G G
fluidigm.208	-0.6384	C C	C T	T T	A G	G G	A A	0 0
fluidigm.209	9.3177	C C	T T	T T	A G	A G	A A	G G
fluidigm.210	14.8897	C T	T T	T T	A G	0 0	A G	G G
fluidigm.211	4.1557	C C	T T	T T	A A	A G	0 0	G G
fluidigm.212	4.8897	C C	T T	T T	A A	A G	A A	G G

fluidigm.213	-1.1103	C T	C T	T T	A A	G G	A A	G G
fluidigm.214	-1.6384	C C	T T	T T	A A	A G	A A	G G
fluidigm.215	-8.1103	C T	C T	T T	A A	A G	A A	G G
fluidigm.216	1.2420	C C	C T	T T	A A	G G	A A	G G
fluidigm.217	6.0958	C C	C C	T T	A G	G G	A A	G G
fluidigm.218	9.8345	C C	C T	T T	A G	G G	A A	G G
fluidigm.219	-9.7580	C C	T T	T T	A A	A G	A G	G G
fluidigm.220	8.2804	C C	T T	T T	A A	G G	A A	G G
fluidigm.221	-8.6384	C C	C T	T T	A A	G G	A A	G G
fluidigm.222	5.8897	C C	C C	T T	A A	A G	A A	G G
fluidigm.223	4.8897	C C	C C	T T	G G	G G	A A	G G
fluidigm.224	-0.7580	C C	C C	T T	A G	G G	A G	G G
fluidigm.225	7.3177	C T	C T	C T	A G	A G	A A	G G
fluidigm.226	-14.1103	C C	T T	T T	A A	A G	A A	G G
fluidigm.227	-0.1103	C C	T T	T T	A G	A G	A A	G G
fluidigm.228	-1.9153	C C	T T	T T	A A	A G	A A	G G
fluidigm.229	-3.5680	C C	T T	T T	A A	G G	A A	G G
fluidigm.230	3.2420	C T	C T	T T	A A	A G	A A	C G
fluidigm.231	9.3177	C C	C C	T T	A A	G G	A A	G G
fluidigm.232	-1.5680	C C	T T	T T	A A	G G	A A	G G
fluidigm.233	-15.9042	C C	C T	T T	A G	A G	A G	G G
fluidigm.234	4.2804	C C	C C	T T	A A	A G	A A	G G
fluidigm.235	4.2804	C C	C C	C T	A A	A A	A A	G G
fluidigm.236	5.3177	C C	C C	T T	A G	G G	A A	G G
fluidigm.237	-2.6384	C C	C C	T T	A G	G G	A A	C G
fluidigm.238	6.0847	C C	T T	T T	A A	G G	A G	G G
fluidigm.239	3.0847	C C	C T	T T	A G	A G	A A	G G
fluidigm.240	0.2804	C T	C T	T T	A A	A G	A A	C G
fluidigm.241	-14.7580	C C	C T	T T	A A	A G	A G	G G
fluidigm.242	-2.7196	C C	C T	T T	A G	G G	A G	G G
fluidigm.243	2.1557	C C	T T	T T	A G	G G	A A	G G
fluidigm.244	13.2420	C C	C T	T T	A G	A A	A A	C G
fluidigm.245	-28.9042	C C	C T	T T	A G	G G	A A	G G
fluidigm.246	6.2420	C T	C T	T T	A A	A G	A G	G G
fluidigm.247	5.1885	C C	C T	C T	A G	A A	A A	G G
fluidigm.248	3.2804	C C	C T	T T	A A	A G	A A	G G
fluidigm.249	3.8897	C C	T T	T T	A G	A G	A G	G G
fluidigm.250	-1.9153	C C	T T	T T	A A	A G	A A	G G
fluidigm.251	-1.6823	C C	C C	T T	A A	A G	A A	G G
fluidigm.252	2.2804	C C	T T	T T	A A	A A	A A	G G
fluidigm.253	3.2420	C C	C T	T T	A A	G G	A A	G G
fluidigm.254	-8.6384	C T	C C	T T	A A	A G	A G	G G
fluidigm.255	0.4320	C C	C T	T T	A A	G G	A A	G G

fluidigm.256	-24.1103	C C	C T	T T	A A	A G	A A	G G
fluidigm.257	-19.9042	C C	C C	T T	A A	G G	A A	G G
fluidigm.258	-8.9153	C C	C C	T T	A A	G G	A A	G G
fluidigm.259	-4.7580	C C	C T	T T	A G	A G	A A	G G
fluidigm.260	0.2420	C C	T T	T T	A G	G G	A A	C G
fluidigm.261	-0.6384	C C	C T	T T	A A	G G	A G	G G
fluidigm.262	0.0958	C C	C T	T T	A A	A G	A A	G G
fluidigm.263	3.8897	C C	T T	C T	A A	G G	A G	G G
fluidigm.264	-10.1103	C C	C T	T T	A A	A G	A A	G G
fluidigm.265	10.4320	C C	C C	T T	A G	A G	A A	G G
fluidigm.266	4.2804	C C	T T	T T	A A	A G	A A	C G
fluidigm.267	-8.9042	C C	C C	T T	A A	A A	A A	G G
fluidigm.268	2.2804	C C	C T	T T	A A	G G	A A	G G
fluidigm.269	12.0958	C C	T T	T T	A A	G G	A A	C G
fluidigm.270	-3.3841	C C	C T	T T	A G	A G	A A	C G
fluidigm.271	-1.7580	C C	T T	T T	A A	A A	A A	G G
fluidigm.272	8.3177	C C	C T	T T	A A	G G	A A	G G
fluidigm.273	1.8897	C C	C T	T T	A G	A A	A G	G G
fluidigm.274	-0.1103	C C	C T	T T	A A	G G	A G	G G
fluidigm.275	2.3177	C C	C T	T T	A A	A G	A A	C G
fluidigm.276	0.3616	C C	T T	T T	A G	A G	A G	G G
fluidigm.277	6.4320	C T	C T	T T	A G	G G	A A	G G
fluidigm.278	11.0958	C C	T T	T T	A A	A G	A G	G G
fluidigm.279	4.8897	C C	C T	T T	A A	A G	A A	C G
fluidigm.280	0.3177	C C	C C	T T	A A	G G	A A	G G
fluidigm.281	-2.7580	C C	T T	C T	A G	G G	A A	G G
fluidigm.282	1.8897	C C	C T	T T	A A	A A	A A	G G
fluidigm.283	-8.1103	C C	C C	T T	A G	A G	A G	G G
fluidigm.284	11.3616	C C	T T	T T	A G	A A	A A	C G
fluidigm.285	1.2804	C T	C T	C T	A G	A G	A A	G G
fluidigm.286	-1.7580	C C	C T	T T	A A	A G	A A	G G
fluidigm.287	6.9687	C C	C C	T T	A G	G G	A A	G G
fluidigm.288	5.9687	C C	C C	T T	A A	G G	A G	G G
fluidigm.289	4.4320	C C	C T	T T	A G	A G	A A	G G
fluidigm.290	3.3177	C C	C T	T T	A A	G G	A A	G G
fluidigm.291	-2.7196	C C	T T	T T	A G	A G	A A	G G
fluidigm.292	-6.1103	C C	C T	T T	A G	A G	A G	G G
fluidigm.293	-0.7580	C C	C C	T T	A A	A G	A A	G G
fluidigm.294	-1.5680	C C	T T	T T	A G	A G	A A	G G
fluidigm.295	-8.6823	C C	T T	T T	A A	G G	A A	G G
fluidigm.296	3.2420	C C	T T	T T	A A	A A	A A	G G
fluidigm.297	-1.9153	C C	C T	T T	A A	G G	A A	G G
fluidigm.298	2.1885	C C	T T	T T	A G	A A	A A	G G

fluidigm.299	0.3177	C C	C C	T T	A A	A A	A A	G G
fluidigm.300	-2.6823	C C	C T	T T	A A	A G	A G	G G
fluidigm.301	3.2420	C C	C T	T T	A A	A A	A A	G G
fluidigm.302	-9.1103	C C	C C	T T	A A	A A	A A	G G
fluidigm.303	4.3177	C C	C T	T T	A A	A G	A G	G G
fluidigm.304	0.2804	C C	T T	T T	A A	G G	0 0	G G
fluidigm.305	5.4320	C C	0 0	T T	A A	G G	0 0	G G
fluidigm.306	0.0781	C C	C T	T T	A A	G G	A A	G G
fluidigm.307	1.8897	C C	C C	T T	G G	A A	A A	G G
fluidigm.308	-6.1103	C C	C C	T T	A A	A G	A G	G G
fluidigm.309	10.4320	C C	C C	T T	A A	G G	A A	G G
fluidigm.310	-2.9153	C C	C T	T T	A A	A A	A A	G G
fluidigm.311	13.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.312	1.4320	C C	C T	T T	A A	G G	A A	G G
fluidigm.313	4.4320	C T	C T	T T	A A	A G	A A	G G
fluidigm.314	12.0958	C C	T T	T T	A G	G G	A A	G G
fluidigm.315	2.8897	C C	T T	T T	A G	A A	A A	G G
fluidigm.316	1.0847	C C	C T	T T	A A	G G	A A	G G
fluidigm.317	-6.7580	C C	C T	T T	A A	A A	A G	G G
fluidigm.318	-24.1103	C C	C T	T T	A G	A G	A A	G G
fluidigm.319	-3.6823	C C	C C	T T	A G	A G	A A	C G
fluidigm.320	1.9847	C C	C T	T T	A A	A G	A G	G G
fluidigm.321	3.2420	C C	T T	T T	A G	A A	A A	G G
fluidigm.322	-18.9153	C C	C T	T T	A A	G G	A A	G G
fluidigm.323	3.2420	C C	T T	T T	A G	G G	A A	C G
fluidigm.324	-0.7580	C T	C T	T T	A A	G G	A G	G G
fluidigm.325	0.3177	C C	C T	T T	A A	G G	G G	C G
fluidigm.326	-2.7580	C C	T T	T T	A A	G G	A A	G G
fluidigm.327	4.0781	C C	T T	T T	A G	A G	G G	G G
fluidigm.328	-2.7196	C C	C C	T T	A G	A A	A A	G G
fluidigm.329	-11.5680	C C	C T	T T	A G	G G	A A	G G
fluidigm.330	6.2804	C C	C C	T T	A G	A A	A G	G G
fluidigm.331	8.3177	C C	T T	T T	A A	G G	A G	G G
fluidigm.332	6.8897	C C	T T	T T	A A	A G	A A	G G
fluidigm.333	-1.7580	C C	C T	C T	A A	A G	A A	G G
fluidigm.334	-0.9153	C C	C T	T T	A A	A G	A A	G G
fluidigm.335	-2.7196	C C	T T	C T	A A	A G	G G	G G
fluidigm.336	-3.6823	C C	C T	T T	A A	G G	A A	G G
fluidigm.337	10.3177	C C	C C	T T	A A	G G	A A	G G
fluidigm.338	-17.6823	C C	C T	T T	A A	A G	A A	C G
fluidigm.339	3.6159	C C	T T	T T	A A	A G	A A	G G
fluidigm.340	1.2804	C C	T T	T T	A G	A G	A A	G G
fluidigm.341	-4.6823	C C	C C	T T	A G	A A	A A	G G

fluidigm.342	6.4320	C C	T T	T T	A A	A G	A A	G G
fluidigm.343	0.3616	C C	T T	T T	A A	G G	A A	G G
fluidigm.344	1.2420	C T	C T	T T	A A	G G	A G	G G
fluidigm.345	11.3616	C C	T T	T T	A A	A G	A A	G G
fluidigm.346	-6.7580	C T	C T	T T	G G	A A	A A	G G
fluidigm.347	-5.7580	C C	T T	T T	A A	A G	A A	G G
fluidigm.348	-1.0313	C C	C T	T T	A A	A G	A A	G G
fluidigm.349	2.3177	C C	T T	T T	A G	G G	A A	G G
fluidigm.350	9.6159	C C	C T	T T	A G	A A	A A	G G
fluidigm.351	-2.9153	C C	C C	T T	A A	G G	A A	G G
fluidigm.352	-4.7580	C T	T T	C T	A A	A A	A A	G G
fluidigm.353	-1.6823	C C	C T	T T	A A	G G	A A	G G
fluidigm.354	-2.9153	C C	C T	T T	A G	G G	A G	G G
fluidigm.355	17.0847	C C	T T	T T	A A	A G	A A	G G
fluidigm.356	5.6159	C C	C T	T T	A A	G G	A A	G G
fluidigm.357	1.0958	C C	T T	T T	A A	A G	A A	G G
fluidigm.358	1.3177	C C	C T	T T	A A	A G	A G	G G
fluidigm.359	-6.7580	C C	C T	T T	A A	G G	A A	G G
fluidigm.360	2.4320	C C	C T	T T	A G	G G	A A	G G
fluidigm.361	-7.6384	C C	C T	T T	A A	A G	A A	C G
fluidigm.362	0.8897	C C	C C	T T	A A	A A	A A	C G
fluidigm.363	7.8897	C T	T T	T T	A G	A G	A A	G G
fluidigm.364	0.2420	C C	0 0	T T	A A	A G	0 0	G G
fluidigm.365	-10.9042	C C	C T	T T	A A	G G	0 0	G G
fluidigm.366	1.3616	C C	T T	T T	A A	A A	G G	G G
fluidigm.367	13.2804	C C	C C	T T	G G	A G	A A	C G
fluidigm.368	-13.7196	C C	T T	T T	A G	A G	A A	G G
fluidigm.369	-0.5680	C C	C T	T T	A A	G G	A A	G G
fluidigm.370	12.2420	C T	T T	0 0	A A	A A	A G	G G
fluidigm.371	12.3177	C C	C T	T T	A G	0 0	A G	G G
fluidigm.372	-7.6823	C C	T T	T T	A A	A G	A G	G G
fluidigm.373	7.4320	C C	T T	T T	A A	A G	A A	G G
fluidigm.374	13.2804	C C	C C	T T	A A	G G	A A	G G
fluidigm.375	4.8897	C C	T T	T T	A A	A G	A G	G G
fluidigm.376	0.4320	C C	C T	T T	A G	G G	A A	G G
fluidigm.377	2.8897	C C	C T	T T	A A	G G	A A	C G
fluidigm.378	-3.7196	C C	C C	T T	A A	G G	A A	G G
fluidigm.379	-11.5680	C T	C T	T T	A A	A G	A A	G G
fluidigm.380	-5.9042	C C	C T	T T	A A	A A	A A	G G
fluidigm.381	0.4320	C C	T T	T T	A A	G G	A A	G G
fluidigm.382	-8.1103	C C	C T	T T	A A	A A	A A	G G
fluidigm.383	3.3616	C C	C T	T T	A A	A G	A G	G G
fluidigm.384	8.9687	C C	C T	T T	A A	A A	A A	G G

fluidigm.385	-5.6384	C T	C T	T T	A G	A G	A A	G G
fluidigm.386	8.6159	C C	T T	T T	A A	A A	A A	G G
fluidigm.387	-6.7196	C C	C C	C T	A A	G G	A G	G G
fluidigm.388	-5.0313	C C	T T	C T	A A	A G	A A	G G
fluidigm.389	-8.5680	C C	C T	T T	A A	A G	A A	G G
fluidigm.390	-1.7196	C C	C T	T T	A A	G G	A A	C G
fluidigm.391	8.2420	C C	T T	T T	A A	G G	A A	G G
fluidigm.392	-1.1103	C T	T T	T T	A G	A G	A A	G G
fluidigm.393	1.8897	C T	C T	T T	A A	A A	A A	C G
fluidigm.394	5.0958	C C	C C	T T	A A	A G	A A	G G
fluidigm.395	6.3177	C C	T T	C T	A G	G G	A A	C G
fluidigm.396	8.3177	C C	C T	C T	A G	A G	A A	G G
fluidigm.397	-14.0313	C C	C C	C T	A A	A G	A A	G G
fluidigm.398	7.3616	C C	C T	T T	A G	G G	A A	G G
fluidigm.399	-8.7196	C C	C T	T T	A G	G G	A G	G G
fluidigm.400	8.6159	C C	C C	T T	A A	A G	A A	G G
fluidigm.401	-19.5680	C C	C T	T T	A A	G G	A A	G G
fluidigm.402	8.3177	C C	C T	T T	A G	A G	A A	G G
fluidigm.403	2.6159	C C	C T	C T	A A	A A	A A	G G
fluidigm.404	-5.0313	C C	C C	T T	A G	G G	A A	G G
fluidigm.405	-1.7196	C C	C T	T T	A A	A G	A A	G G
fluidigm.406	0.4320	C C	T T	T T	A G	A G	A G	G G
fluidigm.407	-3.0313	C C	C T	T T	A A	A G	A G	G G
fluidigm.408	-6.7580	C C	C T	T T	A A	A G	A A	G G
fluidigm.409	-5.3841	C C	C T	T T	A A	G G	A G	G G
fluidigm.410	-5.1103	C C	T T	T T	G G	G G	A A	G G
fluidigm.411	14.0847	C C	C C	T T	A G	G G	A A	G G
fluidigm.412	4.3177	C C	C T	T T	A A	A A	A A	G G
fluidigm.413	5.0958	C C	C T	T T	A A	A G	A A	G G
fluidigm.414	4.2420	C C	C T	T T	A A	A A	A G	G G
fluidigm.415	0.6159	C C	C T	T T	A G	A G	A G	G G
fluidigm.416	8.1557	C C	T T	T T	A A	A A	A A	G G
fluidigm.417	-18.5680	C C	C T	T T	A G	G G	A A	G G
fluidigm.418	3.2420	C C	C T	T T	G G	A G	A A	G G
fluidigm.419	4.3616	C T	C T	T T	A A	A G	A A	G G
fluidigm.420	6.0781	C C	C C	T T	A A	A G	A A	G G
fluidigm.421	5.3616	C C	C T	T T	A A	A G	A A	G G
fluidigm.422	3.2804	C C	T T	C T	A A	A G	A A	G G
fluidigm.423	4.6159	C C	C T	T T	A A	G G	A A	G G
fluidigm.424	9.3616	C C	C T	T T	A G	A G	A A	G G
fluidigm.425	-12.7196	C C	C T	T T	A A	A A	A A	G G
fluidigm.426	2.2420	C C	C T	T T	A G	G G	A A	G G
fluidigm.427	1.1557	C T	C T	T T	A G	A G	A G	G G

fluidigm.471	4.1557	C C	C T	T T	A A	A G	A A	G G
fluidigm.472	17.3177	C C	T T	T T	A A	G G	A G	G G
fluidigm.473	10.3177	C C	C T	T T	A A	A G	A A	G G
fluidigm.474	0.2804	C C	C T	T T	A G	G G	A A	G G
fluidigm.475	-4.6384	C C	C T	T T	A G	A G	A A	G G
fluidigm.476	-14.7196	C C	T T	T T	A A	A A	A A	G G
fluidigm.477	-3.3841	C C	C T	T T	A G	A G	A G	G G
fluidigm.478	3.8897	C T	T T	T T	A A	A G	A A	G G
fluidigm.479	-10.7580	C C	C T	T T	A G	G G	A A	G G
fluidigm.480	4.8897	C C	T T	T T	A A	A G	A A	G G
fluidigm.481	-2.1103	C C	C T	T T	G G	G G	A G	G G
fluidigm.482	-5.6823	C T	C T	T T	A G	G G	A A	G G
fluidigm.483	13.0958	C C	T T	T T	A G	G G	A A	G G
fluidigm.484	-4.1103	C C	C C	T T	A A	A G	A A	G G
fluidigm.485	-1.1103	C C	C T	T T	A A	G G	A A	G G
fluidigm.486	-0.6384	C C	T T	T T	A A	A G	A A	G G
fluidigm.487	7.4671	C C	C T	T T	A A	G G	A A	G G
fluidigm.488	-10.9042	C C	C T	T T	A G	A G	A A	G G
fluidigm.489	-0.5680	C C	T T	T T	A A	A G	A G	C G
fluidigm.490	9.0958	C C	C T	T T	A A	G G	A A	G G
fluidigm.491	-5.9042	C C	C C	T T	A A	G G	A A	G G
fluidigm.492	-1.8443	C C	C T	T T	A G	A G	A A	G G
fluidigm.493	-18.7196	C C	C T	T T	A A	G G	A A	G G
fluidigm.494	5.3616	C C	C T	T T	A A	A A	A A	G G
fluidigm.495	-1.5680	C C	T T	T T	A A	A G	A A	G G
fluidigm.496	-6.7580	C C	T T	T T	A A	A G	A A	G G
fluidigm.497	5.0958	C C	T T	T T	A A	A G	A A	G G
fluidigm.498	-1.9153	C C	T T	T T	G G	A A	A A	G G
fluidigm.499	-2.3841	C C	C T	T T	A A	A G	A A	G G
fluidigm.500	-2.6823	C C	C C	T T	A A	G G	A G	G G
fluidigm.501	-10.6823	C C	C T	T T	A A	A G	A A	G G
fluidigm.502	-6.7580	C T	T T	C T	A A	A G	A A	G G
fluidigm.503	5.2420	C C	C T	T T	A A	A G	A G	G G
fluidigm.504	7.2420	C C	C T	T T	A G	A G	A G	G G
fluidigm.505	4.6159	C C	C T	T T	A A	G G	A A	G G
fluidigm.506	-1.7580	C C	C T	T T	A A	A G	A G	G G
fluidigm.507	8.3177	C C	C T	T T	A G	G G	A G	G G
fluidigm.508	-11.6823	C C	T T	T T	A A	A G	A A	G G
fluidigm.509	-14.1103	C C	C C	T T	A A	G G	A A	C G
fluidigm.510	-1.6384	C C	C T	T T	A A	G G	A A	G G
fluidigm.511	-0.9219	C C	C T	T T	A G	G G	0 0	G G
fluidigm.512	2.2804	C C	C T	T T	A A	A A	A A	G G
fluidigm.513	-7.7580	C C	C T	T T	A A	G G	A A	G G

fluidigm.514	-10.7196	C C	T T	T T	A A	G G	A G	G G
fluidigm.515	9.2420	C C	T T	T T	A G	A G	A A	G G
fluidigm.516	6.8897	C C	T T	T T	A A	G G	A A	G G
fluidigm.517	-3.6823	C C	C T	T T	A A	G G	A G	G G
fluidigm.518	3.2420	C T	C C	T T	A G	A G	A A	G G
fluidigm.519	1.3616	C C	C T	T T	A A	A G	A G	G G
fluidigm.520	-4.5680	C C	C T	T T	A A	A G	A G	G G
fluidigm.521	2.4320	C C	T T	T T	A A	G G	A A	G G
fluidigm.522	-5.6823	C C	C T	T T	A A	A A	A A	G G
fluidigm.523	-9.6823	C C	C T	T T	A G	A G	A G	C G
fluidigm.524	3.0958	C C	C C	T T	A A	G G	A A	C G
fluidigm.525	-0.5680	C C	C C	T T	A G	A A	A A	C G
fluidigm.526	1.2420	C C	T T	T T	G G	A A	A A	G G
fluidigm.527	7.1557	C C	C T	T T	A A	A G	A A	G G
fluidigm.528	6.2420	C C	C T	T T	A G	G G	A A	G G
fluidigm.529	4.2420	C C	C C	T T	A A	A G	A A	G G
fluidigm.530	9.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.531	-10.1103	C C	T T	T T	A G	A G	A A	G G
fluidigm.532	2.8897	C C	C T	T T	A G	G G	A G	G G
fluidigm.533	-4.7580	C C	C T	T T	A A	A G	A A	G G
fluidigm.534	10.8897	C C	C T	T T	A A	A G	A A	G G
fluidigm.535	7.3177	C C	C T	T T	A G	A G	0 0	G G
fluidigm.536	4.0847	C T	T T	C T	A G	G G	0 0	G G
fluidigm.537	12.0958	C C	C T	T T	A G	A G	A A	G G
fluidigm.538	5.9847	C C	C C	T T	A G	G G	A A	G G
fluidigm.539	8.2420	C C	C C	T T	A G	0 0	A A	G G
fluidigm.540	4.0781	C C	C T	T T	A G	G G	A A	G G
fluidigm.541	5.8897	C T	C T	T T	A G	A G	A A	G G
fluidigm.542	-5.6384	C C	C T	T T	A A	A G	A G	G G
fluidigm.543	1.6159	C C	C T	C T	A A	G G	A G	G G
fluidigm.544	-1.7580	C C	C T	T T	A A	A A	A A	G G
fluidigm.545	-0.9042	C C	C T	T T	A G	A A	A A	G G
fluidigm.546	3.6159	C C	C T	T T	A A	G G	A A	G G
fluidigm.547	6.4320	C C	T T	T T	A A	G G	0 0	G G
fluidigm.548	-5.7580	C C	C T	T T	A A	A G	A A	G G
fluidigm.549	4.2420	C C	C T	T T	A G	G G	A A	G G
fluidigm.550	0.2804	C C	T T	T T	A A	G G	A A	G G
fluidigm.551	11.3177	C C	C T	T T	A G	G G	A A	G G
fluidigm.552	5.3177	C C	T T	T T	A A	G G	A A	G G
fluidigm.553	8.2420	C C	C T	T T	A A	G G	A G	G G
fluidigm.554	-4.1103	C C	T T	0 0	A A	G G	A A	G G
fluidigm.555	3.2804	C C	C T	T T	A A	A G	A A	G G
fluidigm.556	6.4320	C C	C T	T T	A A	G G	A A	G G

fluidigm.557	-0.7196	C C	T T	T T	A A	A G	A G	G G
fluidigm.558	2.2420	C C	C T	T T	A A	G G	A A	G G
fluidigm.559	0.0847	C C	C T	T T	A A	A G	A G	G G
fluidigm.560	-4.7196	C C	T T	T T	A A	G G	A A	G G
fluidigm.561	-5.9153	C C	C T	T T	A G	A G	A G	G G
fluidigm.562	7.2420	C C	C T	T T	A A	G G	A A	G G
fluidigm.563	-10.1103	C C	C T	T T	A G	A G	A A	G G
fluidigm.564	5.9847	C C	C T	T T	A A	G G	A A	G G
fluidigm.565	-9.5680	C C	T T	T T	A A	A G	A A	G G
fluidigm.566	2.2420	C C	T T	T T	A A	A G	A A	G G
fluidigm.567	0.2804	C C	C T	T T	A A	A G	A A	G G
fluidigm.568	-2.7580	C C	C C	T T	A G	A G	A A	G G
fluidigm.569	3.0958	C T	C T	T T	A G	A G	A A	G G
fluidigm.570	-14.6823	C C	C T	T T	A A	G G	A A	G G
fluidigm.571	-17.5680	C C	C T	T T	A A	G G	A A	G G
fluidigm.572	1.0958	C C	C T	T T	A A	A G	A G	G G
fluidigm.573	-11.7580	C C	T T	T T	A G	A G	A A	G G
fluidigm.574	-6.7580	C C	T T	T T	A G	A G	A A	G G
fluidigm.575	-1.7196	C C	C T	T T	A A	G G	A A	G G
fluidigm.576	11.2420	C C	C T	T T	A A	G G	A A	G G
fluidigm.577	7.4320	C C	T T	T T	A A	A G	A A	G G
fluidigm.578	-1.1103	C C	C C	T T	A G	G G	A G	G G
fluidigm.579	1.3616	C C	C T	T T	A A	A G	A A	G G
fluidigm.580	6.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.581	-16.5680	C C	C C	T T	A G	G G	A A	G G
fluidigm.582	5.6159	C C	T T	T T	A A	G G	A A	G G
fluidigm.583	3.0847	C C	T T	T T	A A	A G	A G	C G
fluidigm.584	-1.7196	C C	T T	T T	A G	A A	A A	G G
fluidigm.585	-0.6823	C C	C T	T T	A A	A A	A A	G G
fluidigm.586	16.0958	C C	C T	T T	A A	G G	A A	G G
fluidigm.587	6.0847	C T	C C	T T	A A	A G	A A	G G
fluidigm.588	1.2420	C T	T T	T T	A A	A A	A A	G G
fluidigm.589	1.3616	C C	C T	T T	A A	A G	A G	G G
fluidigm.590	4.4671	C T	T T	T T	G G	A A	A A	G G
fluidigm.591	3.8897	C C	C C	T T	G G	A G	A A	G G
fluidigm.592	2.3616	C C	T T	T T	A G	A G	A A	G G
fluidigm.593	12.1557	C C	T T	T T	A A	A G	A A	G G
fluidigm.594	3.8897	C C	T T	T T	A G	A A	A A	G G
fluidigm.595	2.0847	C C	T T	T T	A A	A G	A A	G G
fluidigm.596	4.2420	C C	C T	C T	A G	A G	A A	G G
fluidigm.597	-0.9042	C C	C T	T T	A A	A G	A A	G G
fluidigm.598	-6.7196	C C	C C	T T	A A	G G	A A	G G
fluidigm.599	4.2804	C T	C T	T T	A A	A G	A A	C G

fluidigm.60(	-1.6384	C C	T T	T T	A A	G G	A A	G G
fluidigm.601	-1.1103	C C	C C	T T	A A	A G	A G	G G
fluidigm.602	-3.5680	C C	C T	T T	A A	A G	A A	G G
fluidigm.603	-5.6384	C C	C C	T T	A A	A A	A A	G G
fluidigm.604	10.3177	C C	T T	T T	A A	A G	A G	G G
fluidigm.605	-1.6384	C C	C T	T T	A A	A G	A A	G G
fluidigm.606	3.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.607	-7.5680	C C	C C	T T	A A	A A	A A	G G
fluidigm.608	-1.7580	C C	T T	T T	G G	A G	A A	G G
fluidigm.609	3.3177	C C	T T	T T	A G	G G	A G	G G
fluidigm.610	4.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.611	3.1885	C C	C T	T T	A A	A G	A A	G G
fluidigm.612	-3.1103	C C	C T	C T	A A	G G	A A	G G
fluidigm.613	-5.7580	C T	C C	C T	A G	A G	A G	G G
fluidigm.614	-12.1103	C C	C T	T T	A G	G G	A A	G G
fluidigm.615	-7.9042	C C	T T	T T	A A	G G	A A	G G
fluidigm.616	11.8897	C C	T T	T T	A A	A G	A A	G G
fluidigm.617	-3.6823	C C	C T	T T	A A	A G	A A	G G
fluidigm.618	9.8897	C C	T T	T T	A A	A G	A A	G G
fluidigm.619	-1.1103	C C	C C	T T	A A	G G	A A	G G
fluidigm.620	5.8897	C C	C T	T T	A A	A G	A G	G G
fluidigm.621	6.0847	C C	C T	T T	A A	A G	A A	G G
fluidigm.622	14.3616	C C	T T	T T	A A	0 0	0 0	G G
fluidigm.623	3.0847	C C	C C	T T	A A	A G	0 0	G G
fluidigm.624	4.2420	C T	T T	T T	A G	A G	A A	G G
fluidigm.625	-2.9153	C C	C C	T T	A A	G G	A A	G G
fluidigm.626	0.2420	C C	T T	T T	A A	A G	A A	G G
fluidigm.627	10.9687	C C	T T	T T	A A	A G	A A	G G
fluidigm.628	-3.7196	C C	C T	T T	A A	G G	A G	G G
fluidigm.629	-1.5680	C C	C T	T T	A G	A A	A A	G G
fluidigm.630	3.3177	C C	T T	T T	A A	G G	A A	G G
fluidigm.631	-2.0313	C C	C T	T T	A G	A G	A G	C G
fluidigm.632	9.2804	C C	C T	T T	A A	A A	A A	G G
fluidigm.633	-2.7580	C C	T T	T T	A A	A G	A A	G G
fluidigm.634	-5.1103	C C	C C	C T	A G	G G	A A	G G
fluidigm.635	-0.9042	C C	C C	T T	A A	G G	A A	G G
fluidigm.636	0.3616	C T	T T	T T	A A	A G	A A	G G
fluidigm.637	-2.5680	C C	C T	T T	A A	A G	A G	G G
fluidigm.638	-0.5680	C C	C T	T T	A A	A G	A G	G G
fluidigm.639	12.2420	C C	C T	T T	A A	A G	A A	0 0
fluidigm.640	3.6159	C T	C T	T T	A G	G G	A G	G G
fluidigm.641	11.2804	C C	T T	T T	A A	A G	A G	G G
fluidigm.642	1.1885	C C	C T	T T	A G	G G	A A	G G

fluidigm.643	-0.6823	C C	T T	T T	A G	A G	A A	G G
fluidigm.644	-6.1103	C C	T T	T T	A G	A A	A A	G G
fluidigm.645	-3.1103	C C	C T	T T	A A	0 0	A A	G G
fluidigm.646	-3.1103	C C	C T	T T	A G	G G	A A	G G
fluidigm.647	-6.5680	C C	C C	T T	A G	A G	A G	G G
fluidigm.648	-2.7580	C T	C T	T T	A G	G G	A A	G G
fluidigm.649	15.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.650	1.2804	C C	T T	T T	A G	A G	A A	G G
fluidigm.651	-0.1103	C C	C T	T T	A A	A G	A A	G G
fluidigm.652	3.3616	C C	C T	T T	A A	A G	A A	G G
fluidigm.653	23.0958	C T	C T	T T	A A	A G	A A	G G
fluidigm.654	-0.8115	C C	C T	T T	A A	A G	A A	G G
fluidigm.655	-7.8115	C T	C C	T T	A A	A G	A A	G G
fluidigm.656	3.3616	C T	T T	T T	A A	A G	A G	G G
fluidigm.657	-11.1103	C C	C C	T T	A G	A G	A A	G G
fluidigm.658	8.3177	C T	C T	T T	A G	A G	A A	G G
fluidigm.659	-13.3841	C C	T T	T T	A G	A G	A G	G G
fluidigm.660	6.1557	C C	C C	T T	G G	A G	A A	G G
fluidigm.661	-3.3841	C C	T T	T T	A A	G G	G G	G G
fluidigm.662	-10.1103	C C	C T	T T	A A	A A	A A	G G
fluidigm.663	2.2420	C C	T T	T T	G G	G G	A A	G G
fluidigm.664	5.8897	C C	C T	T T	A A	G G	A A	G G
fluidigm.665	-12.6823	C C	C C	T T	A A	A G	A A	G G
fluidigm.666	10.9687	C C	T T	T T	A A	A G	A A	G G
fluidigm.667	3.4320	C C	T T	T T	A A	A G	A G	G G
fluidigm.668	7.2804	C C	T T	T T	A A	G G	A G	G G
fluidigm.669	4.3616	C C	C T	T T	A A	A G	A A	C G
fluidigm.670	-3.9042	C C	C C	T T	A G	A G	A A	G G
fluidigm.671	8.2420	C C	C T	C T	A A	A A	A A	G G
fluidigm.672	5.9687	C C	C T	T T	A A	G G	A A	G G
fluidigm.673	23.9687	C C	C T	T T	A A	G G	A A	G G
fluidigm.674	1.9687	C C	C T	T T	A A	A G	A G	G G
fluidigm.675	-0.3841	C C	C T	T T	A A	A G	A G	G G
fluidigm.676	1.3177	C C	C T	T T	A G	A G	A A	G G
fluidigm.677	-4.7196	C C	C T	T T	A A	A G	A A	G G
fluidigm.678	-2.5680	C C	C C	T T	A A	A A	A A	G G
fluidigm.679	4.9687	C C	C T	T T	A A	A G	A A	G G
fluidigm.680	0.3177	C C	C T	T T	A A	G G	A G	G G
fluidigm.681	-8.7580	C C	C C	T T	A A	G G	A A	G G
fluidigm.682	17.8345	C C	T T	T T	A G	A G	A A	G G
fluidigm.683	1.2804	C C	T T	T T	A A	A G	A A	G G
fluidigm.684	3.0958	C T	C T	T T	A A	A G	A A	G G
fluidigm.685	5.8897	C C	C T	T T	A A	G G	G G	G G

fluidigm.686	2.3616	C C	T T	C T	G G	A G	A A	G G
fluidigm.687	-4.6823	C C	T T	T T	A A	G G	A G	G G
fluidigm.688	2.3177	C C	C T	T T	A G	A G	A G	C G
fluidigm.689	-17.9042	C C	C T	T T	A A	G G	A A	G G
fluidigm.690	-14.1103	C C	C T	T T	A A	A G	A A	C G
fluidigm.691	4.2804	C C	T T	T T	A A	G G	A A	G G
fluidigm.692	3.2420	C C	C T	C T	A A	G G	A A	G G
fluidigm.693	1.3616	C C	C T	T T	A A	G G	A A	G G
fluidigm.694	-15.1103	C C	C C	T T	A A	G G	A G	G G
fluidigm.695	-2.7196	C C	C C	C T	A A	G G	A A	G G
fluidigm.696	-4.6823	C C	T T	T T	G G	A G	A A	G G
fluidigm.697	2.6159	C C	T T	T T	A G	G G	A A	G G
fluidigm.698	-6.7580	C C	T T	T T	A A	A A	A A	G G
fluidigm.699	4.0958	C C	T T	T T	A A	A G	A A	G G
fluidigm.700	-1.0313	C C	C T	T T	A A	A G	A A	G G
fluidigm.701	-1.7196	C T	C C	C T	A G	A G	A G	G G
fluidigm.702	-6.1103	C C	T T	T T	A G	G G	A A	G G
fluidigm.703	2.8897	C C	C T	T T	A G	A G	A A	G G
fluidigm.704	1.3616	C C	C T	T T	A A	A G	A G	G G
fluidigm.705	-9.1103	C T	C C	T T	A G	A G	A A	G G
fluidigm.706	-10.7196	C T	C C	T T	A G	G G	A G	G G
fluidigm.707	-15.7580	C C	C T	T T	A A	A G	A A	G G
fluidigm.708	-7.9153	C C	C T	T T	A G	G G	A A	G G
fluidigm.709	4.2420	C C	C T	T T	A A	A A	A G	G G
fluidigm.710	2.4320	C C	C T	T T	A A	G G	A A	G G
fluidigm.711	-3.6384	C C	C T	T T	A A	A G	A A	G G
fluidigm.712	-0.5680	C C	T T	T T	A A	G G	A A	G G
fluidigm.713	7.8897	C C	C T	T T	A A	A A	A A	G G
fluidigm.714	2.9687	C C	C T	T T	A A	G G	A A	G G
fluidigm.715	9.3177	C C	C T	T T	G G	G G	A A	G G
fluidigm.716	1.2420	C C	C T	T T	A G	G G	A A	G G
fluidigm.717	1.4320	T T	T T	T T	A G	A A	A A	G G
fluidigm.718	1.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.719	1.8897	C C	C C	T T	A A	A A	A A	G G
fluidigm.720	3.0958	C C	C T	T T	A A	A G	A A	G G
fluidigm.721	-4.9042	C C	C T	T T	A A	G G	A A	G G
fluidigm.722	13.3177	C C	C T	T T	A A	G G	A A	G G
fluidigm.723	2.6159	C C	C C	T T	A A	A A	A G	G G
fluidigm.724	0.2420	C C	C T	T T	A A	A G	A A	C G
fluidigm.725	12.8897	C C	C T	T T	A G	A G	A A	G G
fluidigm.726	-1.7196	C C	T T	T T	A A	A G	A A	G G
fluidigm.727	2.4320	C C	T T	T T	A A	A G	A A	G G
fluidigm.728	-5.6823	C C	T T	C T	A G	G G	A A	G G

fluidigm.729	-7.1103	C C	C T	T T	A G	A A	A G	G G
fluidigm.730	2.1885	C C	C T	T T	A G	G G	A A	G G
fluidigm.731	2.8897	C C	C T	T T	A A	G G	A A	G G
fluidigm.732	0.3177	C C	C T	T T	A A	G G	A A	G G
fluidigm.733	-0.5329	C C	C C	C T	A A	A A	A A	0 0
fluidigm.734	1.2804	C C	C C	T T	A A	G G	A G	C G
fluidigm.735	-7.7580	C C	C T	T T	A G	G G	A A	G G
fluidigm.736	1.2804	C C	T T	T T	A A	G G	A A	G G
fluidigm.737	-0.7196	C C	T T	T T	A A	G G	A A	G G
fluidigm.738	12.3616	C C	C T	T T	A A	A A	A G	G G
fluidigm.739	0.0958	C C	T T	T T	A A	A A	A A	G G
fluidigm.740	-12.1103	C C	C T	T T	A A	A G	A A	G G
fluidigm.741	2.6159	C C	C T	T T	A G	A G	A G	G G
fluidigm.742	-6.5680	C T	C T	T T	A G	A G	A G	G G
fluidigm.743	7.8897	C C	T T	T T	A A	A G	A A	G G
fluidigm.744	5.2420	C C	C T	T T	A G	A A	A A	G G
fluidigm.745	-1.7580	C C	T T	T T	A G	G G	A A	G G
fluidigm.746	-1.1103	C C	C T	T T	A A	G G	A A	G G
fluidigm.747	-2.1103	C C	T T	T T	A A	A G	A A	G G
fluidigm.748	-6.7196	C C	T T	T T	A A	G G	A A	G G
fluidigm.749	4.0847	C C	C T	C T	A A	A A	A G	G G
fluidigm.750	0.1557	C C	C T	T T	A G	G G	A A	G G
fluidigm.751	-7.6384	C C	C T	C T	A A	G G	A A	C G
fluidigm.752	3.0847	C C	T T	T T	A G	A G	A A	G G
fluidigm.753	4.0958	C C	C T	T T	A A	G G	A G	G G
fluidigm.754	-3.7580	C T	T T	T T	G G	A A	A A	G G
fluidigm.755	-6.6823	C C	C C	T T	A A	A G	A A	G G
fluidigm.756	1.4320	C C	T T	T T	A G	A A	A G	G G
fluidigm.757	1.4320	C C	C C	T T	A A	A A	A A	G G
fluidigm.758	-8.1103	C C	C C	T T	A A	A A	A A	G G
fluidigm.759	-2.1103	C C	T T	T T	A G	A A	A A	G G
fluidigm.760	5.9687	C C	C T	T T	A A	A A	A G	G G
fluidigm.761	6.8897	C C	C C	T T	A G	A G	A G	G G
fluidigm.762	-6.9153	C C	C C	T T	A G	A A	A G	G G
fluidigm.763	0.8897	C C	C T	T T	A G	A G	A G	G G
fluidigm.764	4.1885	C T	C C	T T	A A	A G	A A	G G
fluidigm.765	-2.3841	C T	T T	T T	A G	G G	A A	G G
fluidigm.766	-4.6384	C C	C C	T T	A G	A A	A A	G G
fluidigm.767	5.2804	C C	C T	T T	A A	G G	A A	G G
fluidigm.768	11.3177	C C	C T	C T	A G	G G	A A	G G
fluidigm.769	4.2420	C C	T T	T T	A A	G G	A A	G G
fluidigm.770	5.0958	C C	C T	T T	A A	A A	A A	C G
fluidigm.771	-21.7580	C C	T T	T T	A G	G G	A A	C G

fluidigm.772	-13.1103	C C	C T	T T	A A	A A	A A	G G
fluidigm.773	-4.7196	C C	C C	T T	A G	A A	A A	C G
fluidigm.774	0.8897	C C	C C	T T	A A	A A	A A	G G
fluidigm.775	-1.8443	C C	C T	T T	A A	G G	A A	G G
fluidigm.776	-12.9042	C C	T T	C T	A A	A A	A A	G G
fluidigm.777	4.3177	C C	C T	T T	A A	A G	A A	C G
fluidigm.778	4.1885	C C	C T	T T	A A	A G	A G	G G
fluidigm.779	12.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.780	-1.7196	C C	C T	T T	G G	A A	A G	G G
fluidigm.781	13.1557	C C	T T	T T	A A	A G	A A	G G
fluidigm.782	-7.9153	C C	C T	T T	G G	G G	A A	G G
fluidigm.783	-3.9042	C T	T T	C T	A A	A A	A A	G G
fluidigm.784	-2.1103	C C	T T	T T	A A	A A	A A	G G
fluidigm.785	-6.0313	C C	C C	T T	A A	G G	A A	G G
fluidigm.786	12.1557	C C	T T	T T	A A	A G	A A	G G
fluidigm.787	-8.3841	C C	T T	T T	G G	A G	A G	G G
fluidigm.788	-4.6823	C T	C T	C T	A A	A G	A A	G G
fluidigm.789	-3.5680	C C	T T	T T	A A	A G	A A	G G
fluidigm.790	0.8897	C C	C C	T T	A G	A G	A A	C G
fluidigm.791	0.4320	C C	T T	T T	A G	G G	A A	C G
fluidigm.792	-10.1103	C C	C T	T T	A A	0 0	A A	C G
fluidigm.793	-2.6384	C C	T T	T T	A A	A A	A A	G G
fluidigm.794	9.2420	C C	C T	T T	A A	G G	A A	G G
fluidigm.795	-3.5680	C C	T T	T T	A A	G G	A A	G G
fluidigm.796	13.2804	C C	T T	T T	A A	A G	A A	G G
fluidigm.797	4.3616	C C	T T	T T	A G	G G	A A	0 0
fluidigm.798	4.4671	C C	T T	T T	A A	G G	A A	G G
fluidigm.799	-3.6384	C C	T T	T T	A G	G G	A A	G G
fluidigm.800	0.3177	C C	C T	T T	A G	G G	A A	G G
fluidigm.801	5.0958	C C	C T	T T	A A	G G	A A	G G
fluidigm.802	-1.6384	C T	C T	T T	A A	A G	A A	G G
fluidigm.803	11.8897	C C	C T	T T	A G	A G	A A	G G
fluidigm.804	-3.1103	C C	C T	T T	A G	G G	A A	G G
fluidigm.805	19.0958	C C	T T	T T	A G	G G	A G	G G
fluidigm.806	8.8897	C C	T T	T T	A A	A G	A A	G G
fluidigm.807	5.2420	C C	C C	T T	A A	G G	A G	G G
fluidigm.808	9.0958	C C	C T	T T	A A	G G	A A	G G
fluidigm.809	1.3616	C C	T T	T T	A A	G G	A A	G G
fluidigm.810	3.1557	C C	C T	T T	A A	A A	A A	G G
fluidigm.811	3.4671	C C	T T	T T	A G	A G	A A	G G
fluidigm.812	-2.1655	C C	C C	T T	A G	A A	A A	G G
fluidigm.813	11.2804	C C	C T	T T	A G	G G	A A	G G
fluidigm.814	-2.6823	C T	C T	T T	A A	A G	A G	G G

fluidigm.815	5.2420	C C	T T	T T	A G	A A	A A	G G
fluidigm.816	-5.7580	C C	T T	T T	A A	A G	A A	G G
fluidigm.817	-1.9042	C C	C C	T T	A A	A G	A G	G G
fluidigm.818	13.0847	C C	C C	T T	A G	A G	A G	G G
fluidigm.819	14.3177	C C	C T	T T	A A	A A	A A	G G
fluidigm.820	-10.9042	C C	C C	T T	A A	A A	A A	G G
fluidigm.821	11.3177	C C	C C	T T	A A	A G	A A	C G
fluidigm.822	1.9687	C C	C T	T T	A G	A G	A G	G G
fluidigm.823	-0.1103	C C	C T	C T	A A	G G	A A	G G
fluidigm.824	1.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.825	-0.6384	C T	C T	T T	A G	G G	A A	G G
fluidigm.826	-1.3841	C C	C C	T T	A A	A A	A A	G G
fluidigm.827	-1.7580	C T	C T	T T	A G	G G	A A	G G
fluidigm.828	-7.1103	C C	C C	T T	A A	A G	A A	C G
fluidigm.829	1.1885	C C	T T	T T	A A	A A	A A	G G
fluidigm.830	7.2804	C C	T T	T T	A A	G G	A A	G G
fluidigm.831	1.2420	C C	T T	T T	A G	G G	A G	G G
fluidigm.832	3.4320	C C	T T	T T	A G	A A	A G	G G
fluidigm.833	6.3177	C C	C C	T T	A A	A A	A A	G G
fluidigm.834	-0.7580	C C	T T	T T	A A	A A	A G	G G
fluidigm.835	0.0958	C C	C T	T T	A G	A A	A A	G G
fluidigm.836	-13.7580	C C	T T	T T	A A	G G	A A	G G
fluidigm.837	-2.6384	C C	C T	T T	A A	G G	A G	G G
fluidigm.838	9.2804	C C	T T	T T	A A	G G	A G	C G
fluidigm.839	-2.5680	C C	T T	T T	A A	G G	A A	C G
fluidigm.840	-0.6823	C C	T T	T T	A G	G G	A A	C G
fluidigm.841	3.4671	C C	T T	T T	A A	G G	A A	C G
fluidigm.842	0.0847	C C	C T	T T	G G	G G	0 0	G G
fluidigm.843	-3.7580	C C	C T	T T	A A	A G	A A	G G
fluidigm.844	2.0958	C C	C C	T T	A A	A G	A A	G G
fluidigm.845	-26.6823	C C	T T	T T	A A	G G	A A	G G
fluidigm.846	-0.9153	C C	C C	T T	A A	A G	A A	G G
fluidigm.847	8.4320	C C	T T	T T	A A	G G	A A	G G
fluidigm.848	10.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.849	-12.6823	C C	T T	T T	A A	G G	A A	G G
fluidigm.850	-2.7196	C C	C T	T T	A A	A G	A A	G G
fluidigm.851	-4.7196	C C	T T	T T	A A	A G	A A	G G
fluidigm.852	8.8897	C C	C T	T T	A A	A A	A A	G G
fluidigm.853	6.1885	C C	C T	T T	A A	G G	A A	G G
fluidigm.854	-2.7580	C C	T T	T T	A A	G G	A A	G G
fluidigm.855	-8.7196	C C	C T	T T	A A	G G	A A	G G
fluidigm.856	7.6159	C C	C C	T T	A A	A G	A A	G G
fluidigm.857	1.8897	C C	C C	T T	A G	G G	A A	G G

fluidigm.858	11.0958	C C	C T	T T	A A	A A	A A	G G
fluidigm.859	-0.3841	C C	C T	T T	A A	A G	A A	G G
fluidigm.860	-4.1103	C C	C C	T T	A G	A A	A A	C G
fluidigm.861	-2.5680	C C	T T	T T	A G	G G	A A	G G
fluidigm.862	-6.1103	C C	T T	T T	A A	A G	A A	G G
fluidigm.863	0.8897	C C	T T	T T	A A	G G	A A	G G
fluidigm.864	4.0958	C C	C T	T T	A G	A G	A A	G G
fluidigm.865	0.3177	C C	T T	T T	A G	A G	A A	G G
fluidigm.866	-7.3841	C C	C C	T T	A A	G G	A A	G G
fluidigm.867	-0.5680	C C	C C	T T	A G	G G	A A	G G
fluidigm.868	-3.6384	C C	C T	T T	A A	A G	A A	C G
fluidigm.869	-0.7580	C C	C T	C T	A G	G G	A G	G G
fluidigm.870	3.2420	C C	C T	T T	A G	G G	A A	G G
fluidigm.871	-9.5680	C C	T T	T T	A G	G G	A A	C G
fluidigm.872	10.3177	C C	T T	T T	A G	G G	A G	G G
fluidigm.873	0.4320	C C	C T	T T	A A	G G	A A	G G
fluidigm.874	10.2420	C C	C T	T T	A G	G G	A A	G G
fluidigm.875	3.2420	C C	T T	T T	A A	G G	A A	G G
fluidigm.876	-0.0313	C C	C T	T T	A A	A A	0 0	G G
fluidigm.877	5.9847	C C	T T	T T	A A	A G	A A	G G
fluidigm.878	6.3177	C C	C C	C T	A A	A A	A A	G G
fluidigm.879	0.3177	C C	C T	T T	A A	A G	A A	G G
fluidigm.880	11.2804	C T	C T	T T	A A	G G	A A	G G
fluidigm.881	0.2420	C C	C T	T T	A G	A G	A A	G G
fluidigm.882	1.3616	C C	T T	T T	A A	A G	A A	G G
fluidigm.883	-3.3841	C C	C T	T T	A A	G G	A G	G G
fluidigm.884	10.0847	C T	T T	T T	A G	A A	A A	G G
fluidigm.885	-1.6823	C C	C T	T T	A A	A A	A A	G G
fluidigm.886	-9.5680	C T	C T	T T	A A	G G	A A	G G
fluidigm.887	11.6159	C C	C T	T T	A A	G G	A G	G G
fluidigm.888	-8.6823	C C	T T	T T	A A	G G	A A	G G
fluidigm.889	13.0781	C C	C T	T T	A A	A G	A G	C G
fluidigm.890	-14.1103	C C	C T	T T	A A	A A	A A	G G
fluidigm.891	-4.1103	C C	C T	T T	A G	A G	A G	G G
fluidigm.892	6.9847	C C	T T	T T	A A	A G	A A	G G
fluidigm.893	1.8897	C C	C T	C T	A A	G G	0 0	G G
fluidigm.894	2.2420	C C	C T	T T	A G	A G	A A	G G
fluidigm.895	8.3177	C C	C T	T T	A G	G G	A G	G G
fluidigm.896	-0.9042	C C	T T	C T	A A	A G	A A	G G
fluidigm.897	6.2804	C C	C C	T T	A A	A G	A A	G G
fluidigm.898	8.3616	C C	T T	T T	A A	A G	A A	G G
fluidigm.899	-1.8115	C T	C T	T T	A A	A G	A A	G G
fluidigm.900	-25.9042	C C	T T	C T	A G	G G	A A	G G

fluidigm.901	-4.9153	C C	C T	T T	A A	G G	A A	G G
fluidigm.902	4.1557	C C	T T	T T	A A	A G	A A	G G
fluidigm.903	-3.6823	C C	C T	T T	A A	G G	A G	G G
fluidigm.904	-5.6823	C C	C C	T T	A A	A G	A A	G G
fluidigm.905	-3.9042	T T	C T	T T	A A	A G	A A	G G
fluidigm.906	11.8897	C C	T T	T T	A G	A G	A A	C G
fluidigm.907	8.3177	C C	C T	T T	A A	A A	A G	G G
fluidigm.908	1.0847	C C	T T	T T	A A	G G	A A	G G
fluidigm.909	8.3177	C T	T T	T T	A G	A G	A G	G G
fluidigm.910	7.3616	C C	C C	T T	A A	G G	A A	G G
fluidigm.911	2.2420	C C	C C	T T	A A	A G	A A	G G
fluidigm.912	-7.5680	C T	T T	T T	A G	A A	A A	G G
fluidigm.913	-2.6823	C C	T T	T T	A G	A G	A A	G G
fluidigm.914	-5.5680	C C	C T	T T	A G	G G	A A	G G
fluidigm.915	-6.5680	C C	C T	T T	A A	G G	A A	G G
fluidigm.916	-1.9153	C C	T T	T T	A A	G G	A A	G G
fluidigm.917	7.3177	C C	C C	T T	A G	A G	A A	G G
fluidigm.918	1.2420	C C	C T	T T	A A	A A	A A	G G
fluidigm.919	13.2420	C C	C C	T T	A G	G G	A A	G G
fluidigm.920	0.0958	C C	T T	T T	A A	G G	A A	G G
fluidigm.921	13.2420	C C	T T	C T	A A	A A	A A	G G
fluidigm.922	-7.7580	C C	T T	T T	A A	A A	A G	G G
fluidigm.923	-7.7580	C C	T T	T T	A G	A G	A G	G G
fluidigm.924	-5.7196	C C	C T	T T	G G	G G	A A	G G
fluidigm.925	-7.9153	C C	T T	T T	G G	G G	A A	G G
fluidigm.926	0.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.927	3.8897	C C	T T	T T	A A	A G	A G	G G
fluidigm.928	-12.6823	C C	C T	T T	A G	G G	A A	G G
fluidigm.929	1.2420	C C	C T	T T	A A	A A	A A	G G
fluidigm.930	-6.9042	C C	C T	T T	A A	A G	A A	G G
fluidigm.931	-4.6384	T T	C C	T T	A A	G G	A A	G G
fluidigm.932	7.2420	C C	T T	T T	A G	A G	A G	G G
fluidigm.933	0.4320	C C	T T	T T	A A	A G	A A	G G
fluidigm.934	3.4671	C C	C T	C T	A A	G G	A A	G G
fluidigm.935	4.2804	C C	C T	T T	A A	A A	A A	G G
fluidigm.936	2.4320	C T	C T	T T	A A	G G	A A	G G
fluidigm.937	1.0847	C C	C T	T T	A A	G G	A A	G G
fluidigm.938	-1.1103	C C	T T	C T	G G	A G	A A	G G
fluidigm.939	9.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.940	2.8897	C C	C C	T T	A A	G G	A A	G G
fluidigm.941	10.2420	C C	C T	T T	A G	G G	A A	G G
fluidigm.942	12.2420	C C	C T	T T	A A	A A	A A	G G
fluidigm.943	4.2420	C C	C T	T T	A G	G G	A A	G G

fluidigm.944	-1.9042	C C	T T	T T	A A	A G	A A	G G
fluidigm.945	3.8897	C C	C T	T T	A A	A A	A A	G G
fluidigm.946	10.9687	C C	T T	T T	A A	G G	A A	G G
fluidigm.947	0.8897	C C	C C	T T	A A	G G	A A	G G
fluidigm.948	6.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.949	-0.1103	C C	C T	T T	A A	A G	A G	G G
fluidigm.950	-14.1103	C C	T T	T T	G G	A G	A A	G G
fluidigm.951	6.0781	C C	T T	T T	A A	G G	G G	G G
fluidigm.952	13.0958	C C	T T	T T	A A	G G	A A	G G
fluidigm.953	5.3177	C C	T T	T T	A A	A G	A A	G G
fluidigm.954	17.3177	C C	C C	T T	A G	A G	A A	G G
fluidigm.955	13.8897	C C	0 0	T T	A A	A G	A A	G G
fluidigm.956	1.4320	C C	C T	T T	A A	A A	A A	G G
fluidigm.957	-2.8443	C C	C T	T T	A A	A G	A G	G G
fluidigm.958	-8.7580	C C	C T	T T	A A	A A	A A	G G
fluidigm.959	-1.7580	C C	T T	T T	A A	A G	A A	G G
fluidigm.960	-2.6823	C C	C T	T T	A A	G G	A A	G G
fluidigm.961	-3.6384	T T	C C	T T	A A	A A	A A	G G
fluidigm.962	-4.7580	C C	C C	T T	0 0	A G	A A	G G
fluidigm.963	-0.7580	C C	T T	T T	A A	A G	A A	G G
fluidigm.964	-0.7580	C T	0 0	C T	G G	A G	A G	G G
fluidigm.965	-7.7196	C T	C T	T T	0 0	A G	A A	G G
fluidigm.966	-1.3841	C C	C T	T T	A G	A A	A G	G G
fluidigm.967	10.2420	C C	C C	T T	A A	G G	A A	G G
fluidigm.968	12.8897	C C	T T	T T	A A	A G	G G	G G
fluidigm.969	-0.6384	C C	C C	T T	A G	A G	A A	G G
fluidigm.970	3.0958	C C	T T	T T	A G	G G	A A	G G
fluidigm.971	4.0847	C C	C T	T T	0 0	G G	A A	G G
fluidigm.972	-1.5680	C C	0 0	T T	A A	A G	A G	G G
fluidigm.973	3.2804	C C	C T	T T	A G	A G	A G	G G
fluidigm.974	1.0958	C T	C T	T T	A A	G G	A G	G G
fluidigm.975	-3.6823	C C	T T	T T	A G	A A	A A	G G
fluidigm.976	8.8897	C C	C T	T T	A A	A A	A A	G G
fluidigm.977	-6.7580	C T	T T	T T	0 0	G G	A G	G G
fluidigm.978	10.0781	C C	C T	T T	A A	G G	A G	G G
fluidigm.979	-1.6823	C C	T T	C T	G G	A G	A A	G G
fluidigm.980	-4.5680	C C	T T	T T	A G	A G	A A	C G
fluidigm.981	-4.6384	C C	T T	T T	A G	G G	A A	C G
fluidigm.982	-5.7196	C C	C T	T T	G G	G G	A G	G G
fluidigm.983	0.8897	C C	T T	T T	A A	G G	A A	G G
fluidigm.984	1.8897	C C	0 0	T T	A A	G G	A A	G G
fluidigm.985	0.8897	C C	C T	T T	A G	G G	A A	G G
fluidigm.986	-13.7580	C C	C C	T T	A A	G G	A A	G G

fluidigm.987	12.3177	C C	C T	T T	A G	A A	A A	G G
fluidigm.988	-8.3841	C T	0 0	T T	A A	A G	A A	C G
fluidigm.989	-6.5680	C C	C C	T T	A A	A A	0 0	G G
fluidigm.990	-1.6384	C C	T T	C T	A A	G G	0 0	G G
fluidigm.991	11.0958	C C	C T	T T	0 0	A G	A A	G G
fluidigm.992	2.8897	C C	0 0	T T	A A	G G	A A	G G
fluidigm.993	3.9847	C C	T T	C T	A G	A G	A A	G G
fluidigm.994	-12.6823	C C	C C	T T	A A	G G	A A	G G
fluidigm.995	-1.5680	C C	T T	T T	A G	A G	A A	G G
fluidigm.996	-5.7580	C C	C T	T T	A G	A G	A A	G G
fluidigm.997	-2.6823	C C	0 0	T T	A G	G G	A G	G G
fluidigm.998	-12.9042	C C	C T	T T	A A	A G	A A	0 0
fluidigm.999	-6.9042	C C	T T	T T	A G	A G	A A	G G
fluidigm.100	-2.3841	C C	C C	T T	A A	A A	A A	G G
fluidigm.100	14.3616	C C	C C	C T	A G	A G	A A	G G
fluidigm.100	3.1557	C C	C C	T T	A G	A G	A A	G G
fluidigm.100	4.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.100	6.0958	C C	C T	T T	A G	A G	A A	G G
fluidigm.100	0.2804	C C	C T	T T	A A	G G	A A	G G
fluidigm.100	-5.1103	C C	0 0	T T	A A	A G	A A	G G
fluidigm.100	6.0958	C C	T T	T T	A G	A G	A G	G G
fluidigm.100	-1.7580	C C	C T	T T	A G	A G	A A	G G
fluidigm.100	0.8897	C C	C T	T T	A A	G G	A G	G G
fluidigm.101	0.1557	C C	T T	T T	A A	A G	A A	G G
fluidigm.101	4.0847	C C	T T	T T	G G	G G	A G	G G
fluidigm.101	10.2420	C C	C T	T T	A G	A G	A A	G G
fluidigm.101	4.0847	C C	0 0	T T	A G	A G	A G	G G
fluidigm.101	0.8897	C C	C T	T T	A A	A A	A A	G G
fluidigm.101	-0.1103	C C	C T	T T	A A	G G	A G	C G
fluidigm.101	-15.9042	C C	C T	T T	A G	G G	A G	G G
fluidigm.101	14.4320	C C	C T	T T	G G	A G	A A	G G
fluidigm.101	-5.5680	C C	C C	T T	A A	A G	A G	G G
fluidigm.101	-6.7196	C C	C C	T T	A A	A G	A A	G G
fluidigm.102	-3.7196	C C	T T	T T	A A	A A	A A	G G
fluidigm.102	12.0847	C C	C T	T T	A A	G G	0 0	G G
fluidigm.102	14.2804	C C	C C	T T	A A	A G	A A	G G
fluidigm.102	3.8897	C C	C T	T T	A A	A A	A A	G G
fluidigm.102	-4.7196	C C	C T	T T	A G	G G	A G	G G
fluidigm.102	7.3177	C C	C T	T T	A G	A G	A A	G G
fluidigm.102	-13.7196	C C	T T	T T	A G	A A	A G	G G
fluidigm.102	0.8897	C C	T T	T T	A A	A A	A A	G G
fluidigm.102	10.9687	C C	C C	T T	A A	A G	A A	G G
fluidigm.102	2.0958	C C	C T	T T	A G	A G	A A	G G

fluidigm.103	1.2804	C C	C C	T T	A G	G G	A G	G G
fluidigm.103	-14.6823	C C	C T	C T	A G	G G	A A	G G
fluidigm.103	2.2804	C C	C C	T T	A G	G G	A A	G G
fluidigm.103	-10.7196	C C	C T	T T	A G	A A	A A	G G
fluidigm.103	-10.7580	C C	C C	T T	A A	A G	A A	G G
fluidigm.103	6.3616	C C	C T	T T	A G	G G	A A	G G
fluidigm.103	-0.6384	C C	C T	T T	A A	G G	A A	G G
fluidigm.103	3.2420	C C	C T	T T	A G	A G	A G	G G
fluidigm.103	-15.9042	C C	C T	T T	A G	A G	A A	G G
fluidigm.103	2.1885	C C	C T	T T	A A	G G	A A	G G
fluidigm.104	1.3616	C C	T T	T T	A A	A A	A A	G G
fluidigm.104	-2.1103	C C	T T	T T	A A	A G	A A	G G
fluidigm.104	5.4320	C C	T T	T T	A A	A G	A A	G G
fluidigm.104	12.4671	C C	T T	T T	A A	A G	A A	G G
fluidigm.104	-3.7196	C C	C T	T T	A A	G G	A A	C G
fluidigm.104	2.0958	C C	T T	T T	A A	A G	A A	G G
fluidigm.104	-2.0313	C C	C T	T T	A A	A G	A A	G G
fluidigm.104	19.3177	C C	C T	T T	A A	G G	A A	G G
fluidigm.104	-7.7196	C C	T T	T T	A A	A G	A A	G G
fluidigm.104	-0.9153	C C	C T	T T	A A	A G	A A	G G
fluidigm.105	-10.7196	C C	C T	C T	A G	A A	A G	G G
fluidigm.105	6.9687	C C	T T	T T	A G	A G	A G	G G
fluidigm.105	-10.6823	C C	C T	T T	A G	A G	A A	G G
fluidigm.105	-6.6384	C C	C C	T T	A A	G G	A A	G G
fluidigm.105	9.2420	C C	C T	T T	A A	G G	A G	G G
fluidigm.105	4.3177	C C	C T	T T	A G	A G	A A	C G
fluidigm.105	0.2804	C C	C T	T T	A A	G G	A G	G G
fluidigm.105	-6.6384	C C	T T	T T	A A	G G	A A	G G
fluidigm.105	21.0958	C C	T T	T T	A A	A G	A A	G G
fluidigm.105	-9.1103	C C	T T	T T	A A	A G	A A	G G
fluidigm.106	-0.9153	C C	T T	T T	A A	G G	A G	G G
fluidigm.106	-6.5680	C C	T T	T T	A G	A G	A A	G G
fluidigm.106	-1.6384	C C	C T	T T	A G	A G	A A	G G
fluidigm.106	8.8345	C C	C C	T T	A A	A G	A A	G G
fluidigm.106	1.3177	C T	C T	T T	A G	G G	A A	G G
fluidigm.106	-1.9153	C C	C C	T T	A A	A G	A A	G G
fluidigm.106	0.3177	C C	C T	T T	A A	G G	A G	G G
fluidigm.106	-4.5680	C C	C T	T T	A A	A G	A A	C G
fluidigm.106	-5.6823	C T	T T	C T	A A	G G	A A	G G
fluidigm.106	-1.7580	C C	T T	T T	A A	A G	A A	G G
fluidigm.107	-8.7580	C T	C T	C T	A A	A A	A A	G G
fluidigm.107	5.2420	C C	C T	T T	A A	A G	A A	G G
fluidigm.107	-2.1103	C C	T T	T T	A A	G G	A A	G G

Table S2. SNPs analyzed in replication samples and for polygenic modification score.
From Fluidigm genotype data, 61 independent SNPs were chosen to be analyzed for polygenic modification score. S
Use of the Fluidigm platform for replication analysis required us to choose 96 SNPs as a single genotyping panel, an
MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium

					Discovery set (GWA)		
SNP	Chromosome	BP (hg19)	Minor allele	Major allele	MAF	ffect size / minor alle	P-value
rs113605276	1	8,623,490	T	C	0.046	-0.83	3.90E-02
rs1146382	1	85,918,101	C	T	0.417	0.65	8.11E-05
rs115068682	1	108,450,969	C	T	0.035	-2.02	4.49E-06
rs45576236	1	112,319,388	G	A	0.194	0.71	1.03E-03
rs3820400	1	168,074,746	A	G	0.388	0.78	1.19E-05
rs10159075	1	204,160,370	G	A	0.091	-0.89	1.88E-03
rs75376497	1	248,086,661	C	G	0.035	-2.05	3.44E-06
rs144741933	2	11,230,267	A	C	0.017	-2.86	4.44E-06
rs4854546	2	69,317,925	G	A	0.109	-0.93	5.22E-04
rs72810940	2	75,555,265	A	G	0.029	2.43	5.88E-07
rs6751149	2	127,924,981	C	T	0.476	0.65	2.20E-05
rs778194	2	137,599,040	C	A	0.469	0.59	4.97E-04
rs13017290	2	202,909,097	C	T	0.477	0.69	3.93E-05
rs17036872	3	12,559,188	A	G	0.167	-0.90	2.54E-05
rs17197692	3	36,775,946	C	A	0.059	-1.38	6.33E-05
rs1799977	3	37,053,568	G	A	0.319	0.90	7.16E-07
rs34625289	3	64,696,009	A	G	0.111	-0.97	1.92E-04
rs1491738	3	68,276,485	T	C	0.286	0.69	7.87E-05
rs2289596	3	111,701,173	C	T	0.207	0.57	1.13E-02
rs7652523	3	171,674,996	C	G	0.389	0.60	7.29E-04
rs7627373	3	190,763,662	A	G	0.168	-0.89	1.03E-04
rs890490	3	196,750,207	A	G	0.197	0.81	4.22E-05
rs77304846	4	70,495,353	C	T	0.182	-0.74	6.14E-04
rs143869898	4	105,077,431	A	G	0.015	-3.05	1.72E-05
rs10005354	4	167,869,220	G	T	0.098	1.07	7.70E-05
rs72713682	4	178,684,282	C	T	0.018	-2.61	1.53E-05
rs12655177	5	2,156,456	T	C	0.108	1.10	1.48E-05
rs7704337	5	113,670,134	G	A	0.266	0.80	2.58E-05
rs79274321	5	121,660,713	A	G	0.058	-1.42	3.70E-05
rs67972044	5	155,987,761	C	G	0.052	-1.67	4.91E-06
rs13157017	5	156,610,285	C	T	0.028	-2.12	2.31E-05
rs115775808	5	159,350,164	T	C	0.023	-2.45	5.59E-06
rs9466071	6	21,392,004	A	G	0.364	0.65	1.49E-04
rs6934819	6	132,095,805	A	C	0.069	-1.49	2.81E-06
rs1247336	6	161,377,557	C	T	0.245	-0.86	2.14E-05
rs917810	7	21,061,360	G	C	0.383	0.74	3.17E-05
rs701280	7	83,533,062	T	C	0.446	-0.44	6.58E-03
rs79959239	7	131,887,315	T	C	0.011	3.18	2.98E-05

rs116940312	8	9,230,961	G	C	0.035	1.92	7.14E-05
rs9325798	8	16,644,586	C	T	0.021	2.41	1.54E-05
rs16896685	8	99,155,532	A	G	0.125	-1.04	2.99E-05
rs34852161	8	103,284,508	A	C	0.083	-1.48	3.43E-07
rs7837873	8	125,225,255	A	G	0.397	0.74	3.54E-05
rs148414929	9	92,077,451	A	G	0.028	-1.74	2.72E-04
rs12412337	10	113,652,642	A	G	0.049	1.53	8.60E-05
rs148942750	11	43,738,055	C	T	0.014	-3.12	6.33E-06
rs150429450	11	58,854,570	G	A	0.023	2.21	5.77E-05
rs481871	11	79,354,702	A	G	0.095	-1.21	8.21E-06
rs10892160	11	117,552,640	G	A	0.194	-0.80	9.95E-05
rs11062045	12	2,098,435	T	A	0.144	1.01	1.42E-05
rs150393409	15	31,202,961	A	G	0.016	-5.55	0.00E-16
rs35811129	15	31,241,346	A	G	0.272	1.38	1.16E-13
rs61064919	16	13,343,332	T	G	0.190	-0.88	2.05E-05
rs16975803	16	23,051,026	T	C	0.363	0.68	6.24E-05
rs1486437	16	51,899,860	G	A	0.116	-1.19	2.03E-06
rs74611520	16	56,981,126	T	G	0.112	1.08	4.51E-05
rs72863909	18	1,700,716	G	C	0.102	-1.07	1.13E-04
rs80324765	18	43,344,674	A	G	0.077	-0.99	2.61E-03
rs6136301	20	18,108,215	T	A	0.055	-1.50	2.07E-05
rs62215296	20	24,564,646	A	G	0.278	0.59	2.31E-03
rs738972	22	33,986,668	C	T	0.205	-0.76	1.29E-04

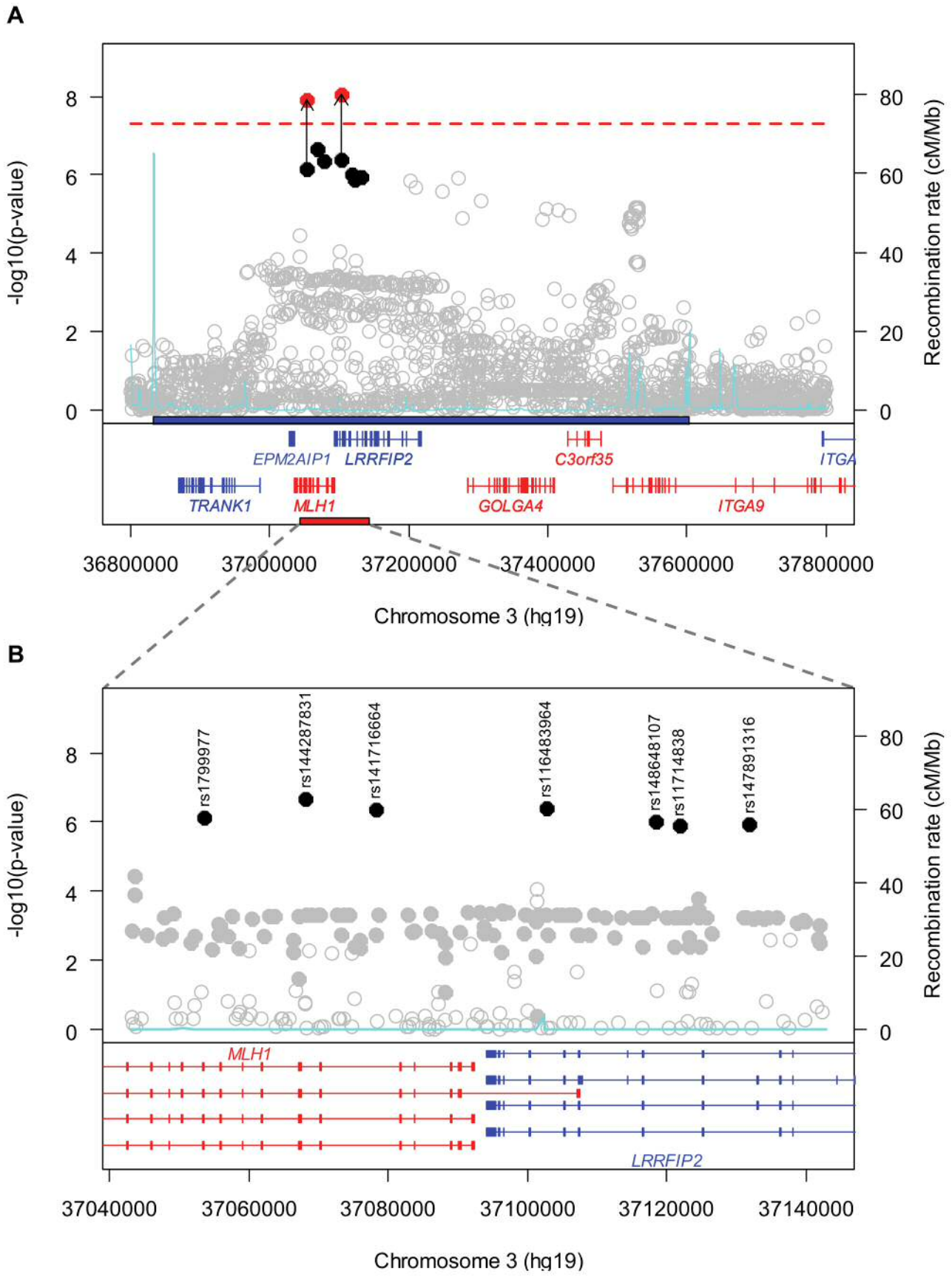
ingle SNP association analysis results in the Fluidigm data are shown.
d therefore we selected SNPs based on relatively relaxed criteria that considered nominal association significance in e

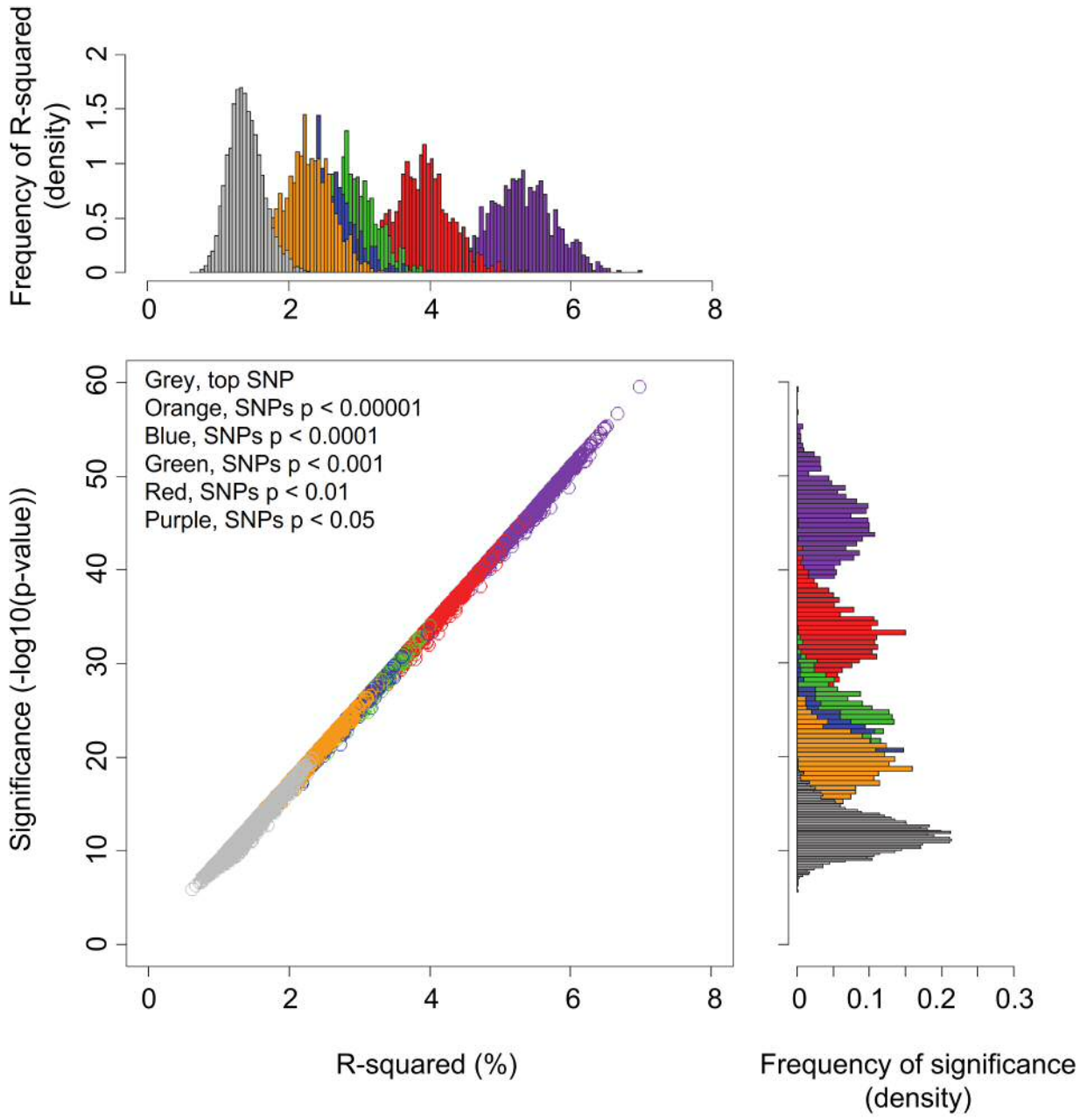
Replication set (Fluidigm)					Meta-analysis	
Call rate (%)	HWE p-value	MAF	ffect size / minor allel	P-value	P-value	Nearest gene(s)
100.0	1.2E-01	0.046	0.09	8.27E-01	1.65E-01	*RERE*
97.2	6.9E-01	0.413	-0.11	5.51E-01	1.08E-02	*DDAH1*
99.7	3.9E-01	0.043	0.02	9.69E-01	7.14E-04	*VAV3*
98.3	2.3E-01	0.178	-0.25	2.93E-01	8.06E-02	*KCND3*
99.4	2.9E-01	0.387	0.00	9.84E-01	1.07E-03	*GPR161*
93.0	2.3E-01	0.090	0.03	9.32E-01	2.20E-02	*KISS1*
99.2	5.8E-01	0.033	-0.39	4.47E-01	7.40E-05	*OR2T8*
99.9	3.1E-01	0.011	-0.02	9.79E-01	6.08E-04	*FLJ33534*
95.7	4.3E-01	0.114	0.68	2.11E-02	2.81E-01	*ANTXR1*
99.9	6.4E-01	0.020	-0.33	6.17E-01	7.32E-04	*TACR1*
99.4	6.2E-01	0.476	0.44	1.62E-02	1.90E-06	*CYP27C1*
97.6	2.6E-01	0.479	-0.04	8.41E-01	1.36E-02	*THSD7B*
99.8	3.3E-01	0.469	-0.11	5.49E-01	7.93E-03	*FZD7*
99.5	7.0E-02	0.153	0.02	9.23E-01	2.16E-03	*TSEN2*
99.5	3.7E-01	0.063	0.16	6.66E-01	7.22E-03	*DCLK3*
99.7	6.8E-01	0.305	0.59	2.58E-03	1.19E-08	*MLH1*
99.5	3.9E-01	0.115	0.17	5.61E-01	1.71E-02	*ADAMTS9-AS2*
98.0	6.1E-01	0.296	0.01	9.56E-01	2.86E-03	*FAM19A1*
97.9	3.6E-02	0.198	0.33	1.39E-01	4.03E-03	*ABHD10*
95.7	9.8E-02	0.381	-0.10	5.99E-01	2.88E-02	*TMEM212-AS1*
98.3	9.5E-01	0.179	0.00	9.96E-01	3.82E-03	*OSTN*
99.3	6.2E-01	0.196	0.03	8.99E-01	1.74E-03	*MELTF*
98.3	6.2E-01	0.171	-0.05	8.50E-01	7.35E-03	*UGT2A1 / UGT2A2*
99.6	1.2E-01	0.006	1.13	3.19E-01	1.14E-02	*CXXC4*
97.7	1.4E-02	0.086	0.06	8.60E-01	2.15E-03	*SPOCK3*
99.5	2.3E-02	0.018	0.03	9.61E-01	1.46E-03	*LINC01098*
99.6	2.7E-01	0.105	0.07	8.06E-01	7.13E-04	*LOC100506858*
100.0	2.5E-01	0.267	-0.12	5.52E-01	6.37E-03	*KCNN2*
94.7	3.9E-01	0.067	0.52	1.64E-01	2.90E-02	*SNCAIP*
99.4	2.6E-01	0.049	-0.03	9.52E-01	5.85E-04	*SGCD*
99.4	1.6E-01	0.025	0.07	8.99E-01	2.19E-03	*ITK*
99.2	3.7E-01	0.020	0.88	1.77E-01	1.32E-02	*ADRA1B*
98.4	5.8E-02	0.361	-0.17	3.53E-01	2.72E-02	*LINC00581*
98.5	2.3E-01	0.062	-0.03	9.37E-01	3.94E-04	*ENPP3*
97.3	4.7E-01	0.244	-0.18	3.94E-01	1.82E-04	*MAP3K4*
98.9	1.7E-01	0.382	0.20	2.85E-01	1.37E-04	*LINC01162*
94.9	8.9E-01	0.452	0.11	5.60E-01	9.74E-02	*SEMA3A*
98.3	1.0E+00	0.010	0.32	7.28E-01	8.22E-04	*PLXNA4*

99.9	2.9E-01	0.027	-0.43	4.46E-01	1.46E-02	*LOC157273*
93.1	2.9E-01	0.027	0.82	1.54E-01	2.70E-05	*FGF20*
98.7	6.3E-01	0.126	-0.08	7.71E-01	9.53E-04	*POP1*
100.0	3.6E-01	0.084	-0.87	7.37E-03	2.39E-08	*UBR5*
97.5	2.8E-02	0.400	-0.10	5.79E-01	6.51E-03	*LOC101927588*
94.3	1.3E-01	0.020	-0.41	5.33E-01	1.63E-03	*SEMA4D*
99.6	8.5E-01	0.048	0.05	9.00E-01	2.67E-03	*GPAM*
99.9	1.0E+00	0.014	0.44	5.80E-01	2.84E-03	*HSD17B12*
99.2	7.7E-01	0.030	-0.54	3.15E-01	2.02E-02	*FAM111B*
99.4	1.9E-01	0.096	0.04	9.02E-01	1.21E-03	*TENM4*
99.0	1.7E-01	0.196	-0.22	3.33E-01	3.94E-04	*DSCAML1*
96.4	7.6E-02	0.146	0.12	6.45E-01	3.77E-04	*DCP1B*
99.0	4.2E-01	0.013	-2.38	3.07E-03	0.00E-16	*FAN1*
99.2	1.4E-01	0.265	1.30	2.09E-10	0.00E-16	*MTMR10*
98.2	4.6E-01	0.193	0.49	3.23E-02	7.97E-02	*SHISA9*
94.7	2.5E-01	0.364	0.27	1.58E-01	8.11E-05	*USP31*
98.9	4.0E-01	0.119	0.03	9.14E-01	5.28E-04	*LINC01571*
99.6	4.9E-02	0.110	-0.41	1.54E-01	3.75E-02	*HERPUD1*
99.6	4.1E-01	0.080	-0.05	8.84E-01	3.00E-03	*LINC00470*
99.5	1.4E-02	0.082	0.10	7.69E-01	4.11E-02	*SLC14A1*
95.5	5.9E-01	0.053	-0.22	5.99E-01	3.97E-04	*PET117*
96.4	4.8E-01	0.277	-0.14	5.00E-01	6.64E-02	*SYNDIG1*
98.3	4.7E-02	0.206	-0.33	1.56E-01	1.44E-04	*LARGE1*

ither the original standard continuous analysis or extreme dichotomous analysis of the discovery data set. Thus, many

SNPs did not generate strong association signals in the replication data set.


A
-log10(p-value)
Recombination rate (cM/Mb)
EPM2AIP1
LRRFIP2
C3orf35
ITGA
TRANK1
MLH1
GOLGA4
ITGA9
36800000
37000000
37200000
37400000
37600000
37800000
Chromosome 3 (hg19)
B
rs1799977
rs144287831
rs141716664
rs116483964
rs148648107
rs11714838
rs147891316
MLH1
LRRFIP2
37040000
37060000
37080000
37100000
37120000
37140000
Chromosome 3 (hg19)


Frequency of R-squared (density)
0
0.5
1
1.5
2
0
2
4
6
8
Grey, top SNP
Orange, SNPs p < 0.00001
Blue, SNPs p < 0.0001
Green, SNPs p < 0.001
Red, SNPs p < 0.01
Purple, SNPs p < 0.05
Significance (-log10(p-value))
0
10
20
30
40
50
60
0
2
4
6
8
R-squared (%)
0
0.1
0.2
0.3
Frequency of significance (density)