**An epigenome-wide meta-analysis of the associations of vitamin B12 concentrations in pregnancy and in newborns with newborn DNA methylation**

*Analysis plan for meta-analysis*

Giulietta S. Monasso, Bonnie R. Joubert, Sandra G. Heil, Vincent W.V. Jaddoe, Stephanie J. London, Janine F. Felix [final order to be determined]

16 April 2020

**Contact details**

For questions and/or joining this meta-analysis: please email Giulietta Monasso ([g.monasso@erasmusmc.nl](mailto:g.monasso@erasmusmc.nl)) or Janine Felix ([j.felix@erasmusmc.nl](mailto:j.felix@erasmusmc.nl))

**BACKGROUND**

Suboptimal vitamin B12 concentrations in pregnancy have been associated with lower birth weight, higher body mass index and lower kidney function in the children (2, 3). Vitamin B12, or cobalamin, is a crucial co-factor in the one-carbon metabolism (OCM), which comprises several interlinking cyclic metabolic pathways essential for cellular growth and differentiation, nucleic acid synthesis and DNA methylation, among others. As such, concentrations of its components *in utero* may affect newborn DNA methylation and subsequently child health (4). A meta-analysis of two epigenome-wide association studies (EWASs) reported that concentrations of folate, another OCM component, in pregnancy were associated with newborn DNA methylation at 443 CpG sites (9). Maternal vitamin B12 concentrations have been associated with global newborn DNA methylation, as well as with local newborn DNA methylation at the Insulin-like growth factor (*IGF2*) promoter (4). Newborn vitamin B12 concentrations have been associated with newborn DNA methylation at the Insulin-like growth factor-binding protein 3 (*IGFBP3*) gene (5). A previous study using a two-step Mendelian Randomization approach found evidence for a causal role for DNA methylation in the association of maternal vitamin B12 concentrations in pregnancy with child IQ (6). There have been no EWAs examining associations of vitamin B12 concentrations in pregnancy or newborns with newborn DNA methylation. All previous studies investigated total vitamin B12 concentrations. However, vitamin B12 is only biologically available if bound to the transport protein transcobalamin, which is the case for 20% of the total vitamin B12 concentration (“active B12”). As such, active B12 might better reflect vitamin B12 status (1).

Genetic variants affecting vitamin B12 metabolism may alter its concentrations. A number of genome-wide association studies have reported associations of single nucleotide polymorphisms (SNPs) with vitamin B12 concentrations (7-10). The strongest signal has been reported for rs602662, located in the Fucosyltransferase 2 (*FUT2*) gene, for which carriers of the A allele have higher vitamin B12 concentrations as compared to carriers of the G allele (8-11).

The overall aim of this study is to examine associations of total and active vitamin B12 concentrations in pregnant women and in newborns with newborn DNA methylation, using an EWAs meta-analysis approach.

**OBJECTIVES**

The primary aims of this study are:

1. To meta-analyze epigenome-wide association studies of maternal total vitamin B12 concentrations during pregnancy and newborn DNA methylation;
2. To meta-analyze epigenome-wide association studies of newborn total vitamin B12 concentrations and newborn DNA methylation;

Secondary aims are:

1. To meta-analyze epigenome-wide association studies of maternal active B12 concentrations during pregnancy and newborn DNA methylation;
2. To meta-analyze epigenome-wide association studies of newborn active B12 concentrations and newborn DNA methylation;
3. To examine if findings from the meta-analyses of maternal and newborn total and active vitamin B12 concentrations with newborn DNA methylation (aims 1-4) are associated with DNA methylation in children and adolescents as well. Details of these analyses will be specified at a later stage.
4. To examine if findings from the meta-analyses of maternal and newborn total and active vitamin B12 concentrations with newborn DNA methylation (aims 1-4) show an interaction with *FUT2* genotype of the newborn. Details of these analyses will be specified at a later stage;

**EXPOSURES**

***Maternal total vitamin B12 concentrations (mat.b12)***

The main exposure of interest is maternal total vitamin B12 concentration during pregnancy (mat.b12) in serum or plasma. If your cohort has measured vitamin B12 concentrations at multiple time points in pregnancy, choose the earliest time point in pregnancy.

***Newborn total vitamin B12 concentrations (newborn.b12)***

As a second exposure, we will study associations of newborn total vitamin B12 concentrations (newborn.b12), measured in serum or plasma, with newborn DNA methylation.

***Maternal active B12 concentrations (mat.active.b12)***

If your cohort has measured active B12 concentrations (mat.active.b12) in mothers, please analyze this exposure as well.

***Newborn active B12 concentrations (newborn.active.b12)***Similarly, if your cohort has measured active B12 concentrations (newborn.active.b12) in newborns, please analyze this exposure as well.

Please analyze concentrations of these four exposures continuously per Standard Deviation (SD) increase (Z-scores). Z-scores for each individual can be calculated as follows:

z(i) = ( x - μ ) / σ

x = concentration of exposure variable of individual i in your dataset

μ = mean value of exposure variable in your dataset

σ = standard deviation of exposure variable in your dataset

So for example for vitamin B12 concentration:

Z-score =

(B12 concentration in the individual – mean B12 concentration in study population) / SD of B12 concentration in study population

If you need any help with calculating Z-scores, please email [g.monasso@erasmusmc.nl](mailto:g.monasso@erasmusmc.nl) and we can provide you with the R code.

The R script (see also the appendix) plots the distribution of your exposures (total and active vitamin B12, for mothers and newborns, if available in your cohort). In Generation R, vitamin B12 concentrations outside the analytical range were recorded as either the lower or the upper limit of the assay, resulting in an odd distribution. Please check the distribution of all exposures. If you see a similar pattern in your cohort, please email [g.monasso@erasmusmc.nl](mailto:g.monasso@erasmusmc.nl), then we can discuss how to handle this. Please do not exclude these cases from your primary analyses. In Generation R, we performed a sensitivity analysis, excluding participants with values outside the limits.

**EXCLUSIONS**

* Exclude mothers and newborns with total vitamin B12 concentrations and active B12 concentrations outside +/- 5 standard deviations from the mean in your dataset.
* Exclude all twins.
* For mothers with multiple children (non-twin siblings), include only one child per mother, based on completeness of data and, if equal, randomly. Please describe in the readme file how many siblings were excluded.

**OUTCOME**

DNA methylation measured using the Illumina Infinium 450k or EPIC arrays in cord blood or newborn blood (spots). QC and normalization can be done using your preferred method and should be described in the readme file. Use untransformed beta-values as outcome measure. Exclude outliers in the methylation values using the 3IQR (Tukey) method. Remove probes on the sex chromosomes. If possible, do not exclude probes because they are listed as possibly problematic (e.g. by Chen or Naeem) at this point. We will do this at the meta-analysis stage.

**COVARIATES**

The covariates are selected based on both literature and a Directed Acyclic Diagram (DAG), see **Figure 1.** Please name all covariates exactly as asked (name defined between brackets for each variable), in order to prevent problems with running the R code.

*Covariates:*

* Maternal age (mat.age): Age at conception. Continuous, in years.
* Maternal socio-economic status (mat.ses): Use the definition most suited in your cohort. Preferably, a three category ordinal variable (1 = lower, 2 = middle, 3 = higher). If you need to categorize mat.ses differently, please inform us.
* Maternal pre-pregnancy BMI (mat.bmi): Continuous in kg/m2.
* Maternal smoking during pregnancy (mat.smoking): binary numeric variable, 0 = no smoking or 1st trimester only (quit before 2nd trimester); 1 = sustained smoking.
* Parity (parity): binary numeric variable, 0 = nulliparous; 1 = multiparous.
* Child sex (sex): binary numeric variable, 0 = boy; 1 = girl.
* Estimated cell types: Use the “Salas” reference set for cell type estimation in the ‘’FlowSorted.CordBlood.Combined.450K’’ or “FlowSorted.CordBlood.Combined.EPIC’’ Bioconductor package for cell type correction. Include the following cell types: CD8T, CD4T, NK, Bcell, Mono, Gran, nRBC (12). If you need a script for estimating these, contact us.
* Batch (batch): Please adjust for batch effects by including the most important covariate(s), such as plate, in the models. Alternatively, you can use a batch correction method such as ComBat. Please indicate in the README file how you adjusted for batch.
* Gestational age at vitamin B12 measurement (gest.age.sampling). Continuous in weeks [only in analyses of maternal total and active B12, this covariate will not be included in analyses of newborn total and active B12].
* Selection factors: optional covariate, include if relevant for your study and describe in the readme file. For example, case-control status if your study was designed as a case-control study.
* Ethnicity: If your study includes more than one major ethnic group (e.g. African, Asian, European or Hispanic) please analyze these groups separately.

*Sensitivity analyses:*

1. Adjustment for Folate

* Maternal folate concentration during pregnancy (mat.folate): continuous in Z-score [only in analysis of maternal total B12, this covariate will not be included in the analysis of newborn total B12]. If your cohort has not measured maternal folate in pregnancy, please set this covariate to NA for all cases. Please only adjust for maternal folate concentration measured in blood; do not adjust for folic acid supplementation/intake in pregnancy. For calculation of Z-scores, see above.
* Newborn folate concentration (newborn.folate): continuous in Z-score [only in analysis of newborn total B12, this covariate will not be included in the analysis of maternal total B12]. If your cohort has not measured newborn folate concentrations, please set this covariate to NA for all cases. For calculation of Z-scores, see above.

1. Adjustment for Homocysteine

* Maternal homocysteine concentration during pregnancy (mat.homocysteine): continuous in Z-score [only in analysis of maternal total B12, this covariate will not be included in the analysis of newborn total B12]. If your cohort has not measured maternal homocysteine in pregnancy, please set this covariate to NA for all cases. For calculation of Z-scores, see above.
* Newborn homocysteine concentration (newborn. homocysteine): continuous in Z-score [only in analysis of newborn total B12, this covariate will not be included in the analysis of maternal total B12]. If your cohort has not measured newborn homocysteine concentrations, please set this covariate to NA for all cases. For calculation of Z-scores, see above.

*Secondary analyses:*

These analyses will be look-ups of any hits found in the analyses described in aims 1-4 in children and adolescents. Also, we will examine for hits found in the analyses described in aims 1-4 show an interaction with *FUT2* genotype of the newborn. We will be in touch about when and how to run these analyses at a later stage.

Childhood/adolescence analyses (whole blood)

Please inform us if your cohort has information on one or more of the exposures and DNA methylation in children/adolescents available.

Analyses stratified on *newborn* genotype:

Stratification of newborns on SNP rs602662 (*FUT2*): AA=0, AG=1, GG=2.

Please inform us if your cohort has genetic information on this SNP available in the offspring. If your cohort does not have genetic information on this particular SNP, please check whether you have a proxy SNP available from the list in **Table 2**, and let us know. If your cohort does have genetic information but not on one of the proxies in **Table 2**, please contact us and we might think about whether we will accept proxy SNPs with lower R^2.

**MODELS**

We will use robust linear regression modelling (rlm) for all analyses and for each CpG site individually. Please run the following models, if available in your cohort, using the syntax provided:

*Maternal vitamin B12 concentrations during pregnancy (continuous, as Z-scores, as described above) and newborn DNA methylation*

1. **Maternal main model**: DNA methylation ~ mat.b12 + gest.age.sampling + mat.age + mat.ses + mat.bmi + mat.smoking + parity + sex + batch +cell types (+selection factors);
2. **Maternal folate model:** DNA methylation ~ mat.b12 + gest.age.sampling + mat.age + mat.ses + mat.bmi + mat.smoking + parity + sex + batch +cell types + *mat.folate* (+selection factors);
3. **Maternal homocysteine model:** DNA methylation ~ mat.b12 + gest.age.sampling + mat.age + mat.ses + mat.bmi + mat.smoking + parity + sex + batch +cell types + *mat.homocysteine* (+selection factors);
4. **Maternal active B12 model**: DNA methylation ~ mat.active.b12 + batch +cell types + gest.age.sampling + mat.age + mat.ses + mat.bmi + mat.smoking + parity + sex (+selection factors);

*Newborn vitamin B12 concentrations (continuous, as Z-scores, as described above) and newborn DNA methylation*

1. **Newborn main model**: DNA methylation ~ newborn.b12 + mat.age + mat.ses + mat.bmi + mat.smoking + parity + sex + batch +cell types (+selection factors);
2. **Newborn folate model:** DNA methylation ~ newborn.b12 + mat.age + mat.ses + mat.bmi + mat.smoking + sex + batch +cell types + *newborn.folate* (+selection factors);
3. **Newborn homocysteine model:** DNA methylation ~ newborn.b12 + mat.age + mat.ses + mat.bmi + mat.smoking + sex + batch +cell types + *newborn.homocysteine* (+selection factors);
4. **Newborn active B12 model**: DNA methylation ~ newborn.active.b12 + mat.age + mat.ses + mat.bmi + mat.smoking + sex + batch +cell types (+selection factors).

**R CODE**

The R script (see also the appendix) to run all models described above is provided at the bottom of this analysis plan. For uniformity of results, please do not use your own script. The script may seem long, but it is a repetition of the same script for each of the models above. That way, all analysts can delete those parts of the script that refer to models that cannot be run in their cohorts, as indicated in the script. If you are not able to run one or multiple models due to missing exposure(s) or covariate(s), please describe this in the read me file. The R script is constructed in a manner that you can easily skip those models you are not able to run (the models are numbered 1-8, as above): just delete those parts of the script with the code for these models. You can easily recognize the start of a new model in the script (full R script in the appendix):

*################### FROM HERE DELETE THOSE PARTS OF THE SCRIPT THAT ARE MEANT TO RUN MODELS YOU CANNOT RUN ###################*

*############################################################## MODEL 1: MATERNAL MAIN MODEL #######################################################*

*## IF MATERNAL TOTAL VITAMIN B12 IS NOT AVAILABLE IN YOUR COHORT, YOU CAN DELETE THIS PART OF THE SCRIPT (UNTIL ##### MODEL 4: MATERNAL ACTIVE B12 MODEL ####)*

If you are not able to run model 2 (maternal folate model) for example, you delete all code in between the line with:

### MODEL 2: MATERNAL FOLATE MODEL ###

and the line with:

### MODEL 3: MATERNAL ACTIVE MODEL ####.

If you are not able to run one or multiple models, please still do construct the complete phenotype file, including all columns, as shown in **Table 1**, but set all missing data in your phenotype file to NA. For example, if your cohort does not have folate measured in newborns, set the variable newborn.folate in the phenotype file to NA for all participants. This procedure makes it unneeded to change the script, just delete the parts of the script used to run the newborn folate model.

The two inputs that you need for the analyses are (for format see **Table 1**):

1. A tab delimited file (e.g. *EWA\_PACE\_B12.dat*) that consists of rows (newborns) and for each newborn four columns with exposures (mat.b12, mat.active.b12, newborn.b12, newborn.active.b12) and the covariates in the subsequent columns as shown in **Table 1**. Please note the following:
   1. Missing values for any of the covariates should be denoted by NA, do not leave any cells blank. The provided R code will exclude these cases for you.
   2. Headers of the columns must be named exactly the same as described in the covariate paragraph above. Do not use quotes around data cells or headers.
   3. The script will automatically make factors of the following covariates: batch, mat.ses, mat.smoking, sex.
   4. If you adjust for batch effect by including more than one covariate, or if you use a batch correction method, you have to adapt the script and phenotype file accordingly. If you need any help with this, please email g.monasso@erasmusmc.nl.
   5. If you have added any selection factor, please add this variable as an extra column to the phenotype file. You also have to change the R script accordingly. If you need any help with this, please email g.monasso@erasmusmc.nl.
2. A matrix of beta values (each column representing a newborn and each column a probe on the array). The script will make sure the newborns are in the same order as in the phenotype file.

**OUTPUT DATA FILE FORMAT**

In the first part of the R script, please specify your cohort name and the date of analysis:

*## Please only change cohort and analysis.date below ##*

*cohort <- "GENR" #change to name of your cohort/study*

*analysis.date <- "20200207" # change to the date (yyyymmdd) at which you perform the analyses*

Then, for each of the models 1-6, the R code will construct a different name for the results file automatically, as follows:

* COHORT \_EXPOSURE\_MODEL\_RESULTS\_DATE.txt
  + COHORT: name of your study
  + EXPOSURE: specifies source of exposure measurement: can be “maternal” or “newborn”
  + MODEL: can be “main”, “folate”, “homocysteine”, “active”
  + DATE: in format YYYYMMDD
  + Examples: GENR\_MATERNAL\_ACTIVE \_RESULTS\_20200210.csv or GENR\_NEWBORN\_MAIN\_RESULTS\_20200315.csv.

Similarly, and with the same format as for the results files, the code will construct a file with the lambda (".lambda.") and file with summary data (".summary.") of each model. If you are not able to run one or multiple models, you don’t have to change anything in the R code, you can just skip/delete the code for that specific model as explained above.

**README FILE**

Please upload a readme file (format: COHORT\_EWAS\_B12\_README\_YYYYMMDD.txt)

containing information on the following:

* Short description of your study/cohort.
* Information on how your exposure(s) and covariates were measured. Please also send us the summary files of all models, these are generated by the R script.
* Subjects in which your cohort has measured vitamin B12: pregnant women and/or their newborns.
* If vitamin B12 has been measured in pregnant women, please inform us at what gestational age the blood has been sampled.
* Material in which your cohort has measured vitamin B12: plasma or serum; cord blood or blood spots.
* Analysis method applied to measure vitamin B12 and/or active B12.
* Information on normalization and QC steps.
* Selection factors, if added to the models.
* If you analyzed multiple ethnic groups separately, please describe.
* Any additional information you think is important to share.
* For each model: lambda and total sample size (the script will provide this information).
* Please inform us about whether your cohort has GWAS data measured in children.
* Please inform us about whether your cohort has DNA methylation data available in childhood and/or adolescents.

**DATA EXCHANGE**

Data can be uploaded to our secure server:

* sftp: im-sftp.erasmusmc.nl
* port: 22
* username: genrupload
* password: connectgenr

Please let us know when you have uploaded your results ([g.monasso@erasmusmc.nl](mailto:g.monasso@erasmusmc.nl))

**TIMELINE (tentative)**

* March 5th: Final analysis plan to PACE
* May 10th: Deadline for uploading results. Any questions can be sent via email to [g.monasso@erasmusmc.nl](mailto:g.monasso@erasmusmc.nl) or [j.felix@erasmusmc.nl](mailto:j.felix@erasmusmc.nl).
* July 10th: QC and meta-analyses conducted
* September 10th: Shadow QC and MA and follow-up analyses conducted
* November 1st: first draft manuscript written

**ACKNOWLEDGEMENTS**

Many thanks to Gemma Sharp for kindly allowing us to use her R code!

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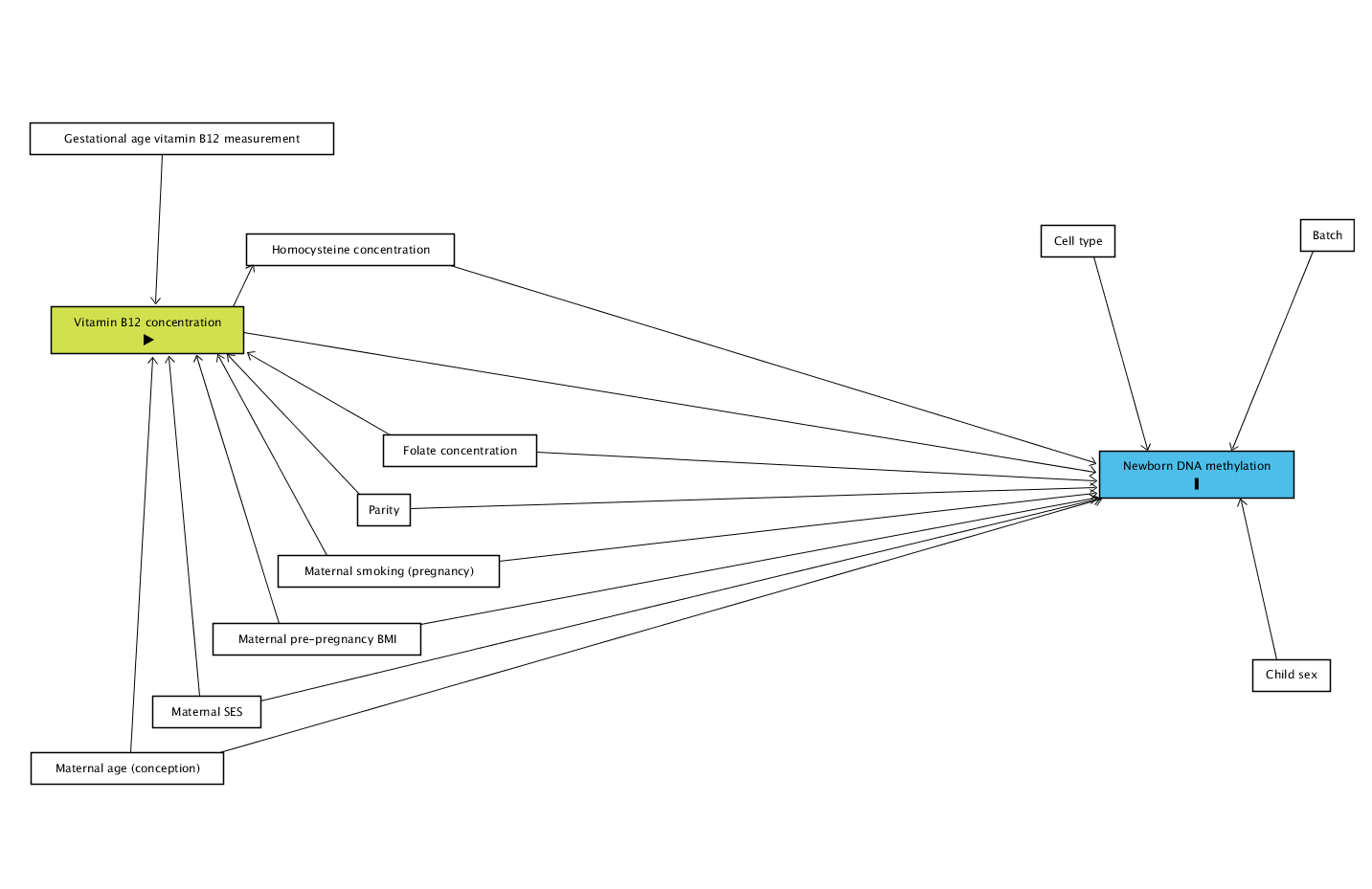


Figure 1 Directed acyclic graph (DAG) represents assumptions of a causal relationship between the exposure (maternal or newborn vitamin B12 concentrations) and outcome (newborn DNA methylation). The other variables shown in the DAG are considered confounders (maternal age, maternal education, maternal smoking, maternal BMI, parity, folate concentration) or factors that influence cord blood methylation (cell type, batch, child sex). Vitamin B12 concentrations change during pregnancy and therefore we adjusted for gestational age at maternal blood sampling (in the maternal models only).

Table 1: phenotype file format (tab delimited (.dat))

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| sample.id | mat.b12 | mat.active.b12 |  | newborn.b12 | newborn.active.b12 | batch | bcell | mono | cd4t | cd8t | gran | nk | nRBC | gest.age.sampling | mat.age | mat.ses | mat.bmi | mat.smoking | Parity | sex | mat.folate | mat.homocystine | Newborn.folate |  | Newborn.homocystine |
| 1234559 | 5.5555 | 0 |  | 5.5555 | 0 | 4 | 0.1340 | 0.3992 | 0.4201 | 0.1104 | 0.1100 | 0.011 | 0.0014 | 80.4032 | 31.3013 | 2 | 20.4544 | 1 | 1 | 0 | NA | -0.03 | NA |  | NA |

Table 2: Proxy list for SNP rs602662 (FUT2) ordered on R2 (highest to lowest)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **RS\_Number** | **Coord** | **Alleles** | **MAF** | **D’** | **R2** |
| rs485186 | chr19:49207206 | (A/G) | 0.4692 | 0.996 | 0.9881 |
| rs485073 | chr19:49207255 | (A/G) | 0.4692 | 0.996 | 0.9881 |
| rs603985 | chr19:49207257 | (T/C) | 0.4692 | 0.996 | 0.9881 |
| rs571689 | chr19:49207554 | (C/T) | 0.4672 | 0.996 | 0.9881 |
| rs570794 | chr19:49207651 | (T/C) | 0.4672 | 0.996 | 0.9881 |
| rs2251034 | chr19:49207792 | (G/A) | 0.4672 | 0.996 | 0.9881 |
| rs506897 | chr19:49208629 | (G/C) | 0.4672 | 0.996 | 0.9881 |
| rs503279 | chr19:49209010 | (T/C) | 0.4672 | 0.996 | 0.9881 |
| rs633372 | chr19:49209226 | (G/A) | 0.4672 | 0.996 | 0.9881 |
| rs504963 | chr19:49208865 | (G/A) | 0.4662 | 0.996 | 0.9841 |
| rs632111 | chr19:49208978 | (A/G) | 0.4662 | 0.996 | 0.9841 |
| rs507855 | chr19:49208501 | (A/G) | 0.4682 | 0.992 | 0.9841 |
| rs507766 | chr19:49208543 | (T/C) | 0.4682 | 0.992 | 0.9841 |
| rs507711 | chr19:49208564 | (C/T) | 0.4682 | 0.992 | 0.9841 |
| rs1688264 | chr19:49209560 | (T/G) | 0.4652 | 0.992 | 0.9723 |
| rs1704773 | chr19:49209566 | (A/G) | 0.4652 | 0.992 | 0.9723 |
| rs2638280 | chr19:49209318 | (G/A) | 0.4702 | 0.988 | 0.9683 |
| rs2548458 | chr19:49209325 | (C/T) | 0.4702 | 0.988 | 0.9683 |
| rs2548459 | chr19:49209339 | (T/C) | 0.4702 | 0.988 | 0.9683 |
| rs692854 | chr19:49209464 | (C/A) | 0.4662 | 0.988 | 0.9683 |
| rs646327 | chr19:49209851 | (A/G) | 0.4682 | 0.98 | 0.9605 |
| rs676388 | chr19:49211969 | (T/C) | 0.4702 | 0.9679 | 0.9295 |
| rs584768 | chr19:49213284 | (G/A) | 0.4692 | 0.964 | 0.9256 |
| rs2452170 | chr19:49213504 | (G/A) | 0.4692 | 0.964 | 0.9256 |
| rs28894750 | chr19:49213531 | (A/T) | 0.4702 | 0.9639 | 0.9218 |
| rs2638282 | chr19:49213833 | (G/A) | 0.4702 | 0.9639 | 0.9218 |
| rs281379 | chr19:49214274 | (G/A) | 0.4602 | 0.9716 | 0.9142 |