

Supplementary information

Supplementary Table 1 - Description of the data sets from the GEO database and used in the present work

GEO ID	Cohort	Disease	Sample Type	Cases			Controls			Reference
				N	Age (years)	Sex (female/male)	N	Age (years)	Sex (female/male)	
GSE153712	Australian Imaging, Biomarkers, and Lifestyle (AIBL)	Alzheimer	blood	161	>60	91/70	471		272/199	NABAIS et al., 2021 ¹
GSE72778	University of California, Los Angeles (UCLA) Brain Research Institute	Alzheimer	brain	18 ^a	58-114	13/5	21 ^b	15-93	6/15	HORVATH et al., 2016 ²
GSE111629	University of Auckland Parkinson's Environment and Gene	Parkinson	blood	335	36 - 90	138/197	237	35-93	111/126	CHUANG et al., 2017 ³
GSE195834		Parkinson	brain	40	70-87	19/21	38	59-87	18/20	VISHWESWARAIAH et al., 2022 ⁴
GSE41273		Fragile X Syndrome	blood	9	01-48	-/9	53	03-18	-/53	ALISCH et al., 2013 ⁵
GSE106648		Multiple Sclerosis	blood	140	16-66	98/42	139	20-65	104/35	KULAR et al., 2018 ⁶

^a Resulting in n= 125 samples (1-12 samples/patient)
^b Resulting in n=135 samples (3-8 samples/patient)

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Supplementary Table 2: Information about the nine hypermethylated CpGs in blood DNA from Alzheimer patients in comparison to healthy controls

CpG	Chr	Gene	CpG_features	padj	Change	deltaBeta (mean)
cg06335143	1	<i>ZYG11A</i>	Body-island	0.00483	Increased	0.02024
cg06639320	2	<i>FHL2</i>	TSS200-island	0.04656	Increased	0.02027
cg07553761	3	<i>TRIM59</i>	TSS1500-island	0.00333	Increased	0.03184
cg06493994	6	<i>SCGN</i>	1stExon-island	0.00002	Increased	0.01559
cg21572722	6	<i>ELOVL2</i>	TSS1500-island	0.00072	Increased	0.01667
cg16867657	6	<i>ELOVL2</i>	TSS1500-island	0.00143	Increased	0.02413
cg24724428	6	<i>ELOVL2</i>	TSS1500-island	0.00229	Increased	0.02455
cg19904058	10	<i>LOC619207</i>	Body-island	0.04629	Increased	0.03305
cg03032497	14		IGR-island	0.03888	Increased	0.02048

Chr: chromosome; CpG_features: CpG position according to “gene-CpG island”; 1stExon: CpG located in the first exon of a gene; TSS1500: 1500 nucleotides upstream of transcription start site; body: gene body; IGR: intragenic region; TSS200: 200 nucleotides upstream of transcription start site; padj: Benjamini-Hochberg adjusted p-value.

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Supplementary Table 3: Information about the nine hypomethylated CpGs in blood DNA from Parkinson patients in comparison with healthy controls

CpG	Chr	Gene	CpG_features	padj	Change	deltaBeta (mean)
cg08347373	2	CD302	Body-shore	0.03992	Decreased	-0.03142
cg25821974	3	RAB7A	5'UTR-shelf	0.00412	Decreased	-0.03642
cg02368812	6	NQO2	3'UTR-opensea	0.00205	Decreased	-0.04215
cg11725581	7		IGR-shelf	0.00069	Decreased	-0.03996
cg17392018	7	CALD1	Body-opensea	0.03992	Decreased	-0.02757
cg14255824	9	TJP2	Body-opensea	0.03992	Decreased	-0.02652
cg21649013	12	ULK1	Body-shore	0.03992	Decreased	-0.01751
cg24904992	17	TBC1D16	5'UTR-shelf	0.04184	Decreased	-0.01578
cg12230709	19	PRTN3	TSS200-shelf	0.00205	Decreased	-0.02571

Chr: chromosome; CpG_features: CpG position according to “gene-CpG island”; body: gene body; 5'UTR located five prime untranslated regions; 3UTR: located three prime untranslated region; IGR: intragenic region; TSS200: 200 nucleotides upstream of transcription start site; padj: Benjamini-Hochberg adjusted p-value.

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Supplementary Table 4: Information about the differentially methylated CpGs in blood DNA from Multiple Sclerosis patients in comparison to healthy controls

CpG	Chr	Gene	CpG_features	padj	Change	deltaBeta (mean)
cg19864490	1	<i>FAM78B</i>	TSS1500-island	0,04544	Increased	0.0082
cg21245277	2	<i>ZNF804A</i>	1stExon-island	0,00990	Increased	0.0112
cg26328180	2		IGR-island	0,03713	Increased	0.0239
cg06027691	3	<i>CTDSPL</i>	Body-opensea	0,00474	Increased	0.0338
cg04521004	3	<i>SHOX2</i>	Body-island	0,01654	Increased	0.0171
cg03427905	3	<i>ADAMTS9</i>	Body-island	0,03290	Increased	0.0112
cg22488278	4	<i>ZFYVE28</i>	Body-opensea	0,00280	Decreased	-0.0282
cg09139047	6	<i>HLA-DRB1</i>	Body-island	0,00280	Increased	0.1619
cg11404906	6	<i>HLA-DRB1</i>	Body-shore	0,00280	Increased	0.1946
cg13910785	6	<i>HLA-DRB1</i>	Body-shelf	0,00280	Decreased	-0.1875
cg17369694	6	<i>HLA-DRB5</i>	3'UTR-opensea	0,00280	Decreased	-0.1579
cg22627029	6	<i>HLA-DRB6</i>	Body-opensea	0,00280	Decreased	-0.1928
cg16514085	6	<i>HLA-DRB1</i>	Body-island	0,00295	Increased	0.1783
cg18111114	6	<i>HLA-DRB5</i>	TSS1500-opensea	0,00295	Decreased	-0.0601
cg00886432	6		IGR-opensea	0,01545	Decreased	-0.0261
cg05383619	6	<i>HLA-DRB1</i>	Body-shore	0,02912	Decreased	-0.0755
cg15708909	6	<i>HLA-DRB5</i>	Body-shelf	0,03290	Increased	0.0703
cg10995422	6	<i>HLA-DRB6</i>	Body-opensea	0,03993	Decreased	-0.1646
cg00119778	6		IGR-opensea	0,04544	Decreased	-0.0151
cg18024368	6	<i>HLA-DQB1</i>	Body-island	0,04544	Increased	0.0260
cg24638099	6	<i>HLA-DRB6</i>	Body-opensea	0,04544	Decreased	-0.0951
cg04671932	7	<i>MAGI2</i>	TSS200-shore	0,03288	Increased	0.0098
cg11592503	7	<i>CNTNAP2</i>	TSS200-island	0,04107	Increased	0.0208
cg26181840	13	<i>RASA3</i>	Body-island	0,01329	Decreased	-0.0204
cg06452665	13	<i>TNFSF11</i>	1stExon-island	0,04590	Increased	0.0213
cg17594334	14	<i>PLEKHH1</i>	5'UTR-island	0,04480	Increased	0.0075
cg16927372	17	<i>ACCN1</i>	Body-shore	0,00474	Decreased	-0.0230
cg10137837	17	<i>BCL6B</i>	5'UTR-island	0,03288	Increased	0.0227

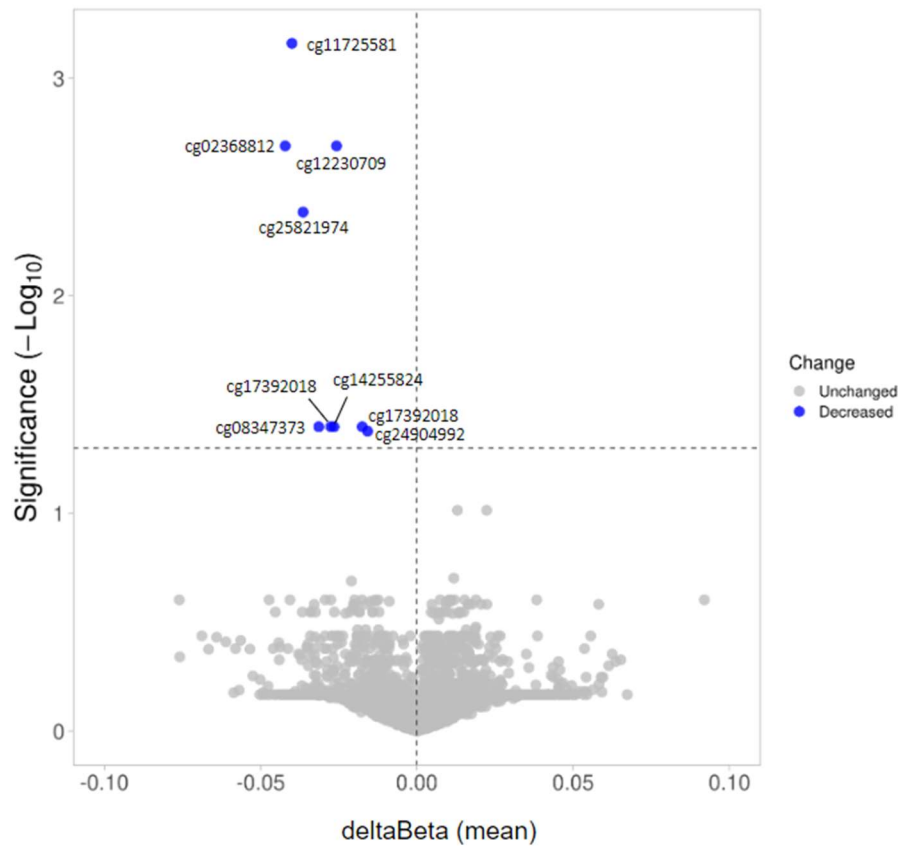
Chr: chromosome; CpG_features: CpG position according to “gene-CpG island”; TSS1500: 1500 nucleotides upstream of transcription start site; 1stExon: CpG located in the first exon of a gene; IGR: intragenic region; body: gene body; 3'UTR: located three prime untranslated regions; 5'UTR located three prime untranslated regions; TSS200: 200 nucleotides upstream of transcription start site; padj: Benjamini-Hochberg adjusted p-value.

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Supplementary Table 5: Information about the differentially methylated CpGs in blood DNA from patients with X Fragile Syndrome in comparison to healthy controls.

CpG	Chr	Gene	CpG_features	padj	Change	deltaBeta (mean)
cg14602222	12	<i>RAD52</i>	Body-opensea	0.01410	Increased	0.1032
cg24678163	13	<i>THSD1P</i>	TSS1500-shore	0.02960	Decreased	-0.0645
cg15116481	19	<i>KLK15</i>	Body-island	0.01830	Decreased	-0.1067
cg02921434	X	<i>ASFMR1</i>	Body-island	0.00000	Increased	0.6979
cg04552106	X	<i>ASFMR1</i>	Body-island	0.00000	Increased	0.7272
cg04744025	X	<i>ASFMR1</i>	Body-island	0.00000	Increased	0.5470
cg05288927	X	<i>ASFMR1</i>	Body-island	0.00000	Increased	0.6189
cg07147350	X	<i>ASFMR1</i>	Body-shore	0.00000	Increased	0.4551
cg08434396	X	<i>ASFMR1</i>	Body-island	0.00000	Increased	0.7164
cg16783314	X	<i>ASFMR1</i>	Body-island	0.00000	Increased	0.6650
cg19741073	X	<i>ASFMR1</i>	Body-island	0.00000	Increased	0.7533
cg21274274	X	<i>ASFMR1</i>	Body-island	0.00000	Increased	0.6061
cg22417678	X	<i>ASFMR1</i>	TSS1500-opensea	0.00000	Decreased	-0.2076
cg22625568	X	<i>ASFMR1</i>	Body-shore	0.00000	Increased	0.6146
cg27064928	X	<i>ASFMR1</i>	Body-shelf	0.00000	Increased	0.3216
cg22675021	X	<i>CTAG2</i>	1stExon-opensea	0.00790	Decreased	-0.1156
cg02055404	X		IGR-island.	0.01710	Increased	0.0439
cg06307153	X	<i>ZNF75D</i>	5'UTR-island	0.04870	Increased	0.0695

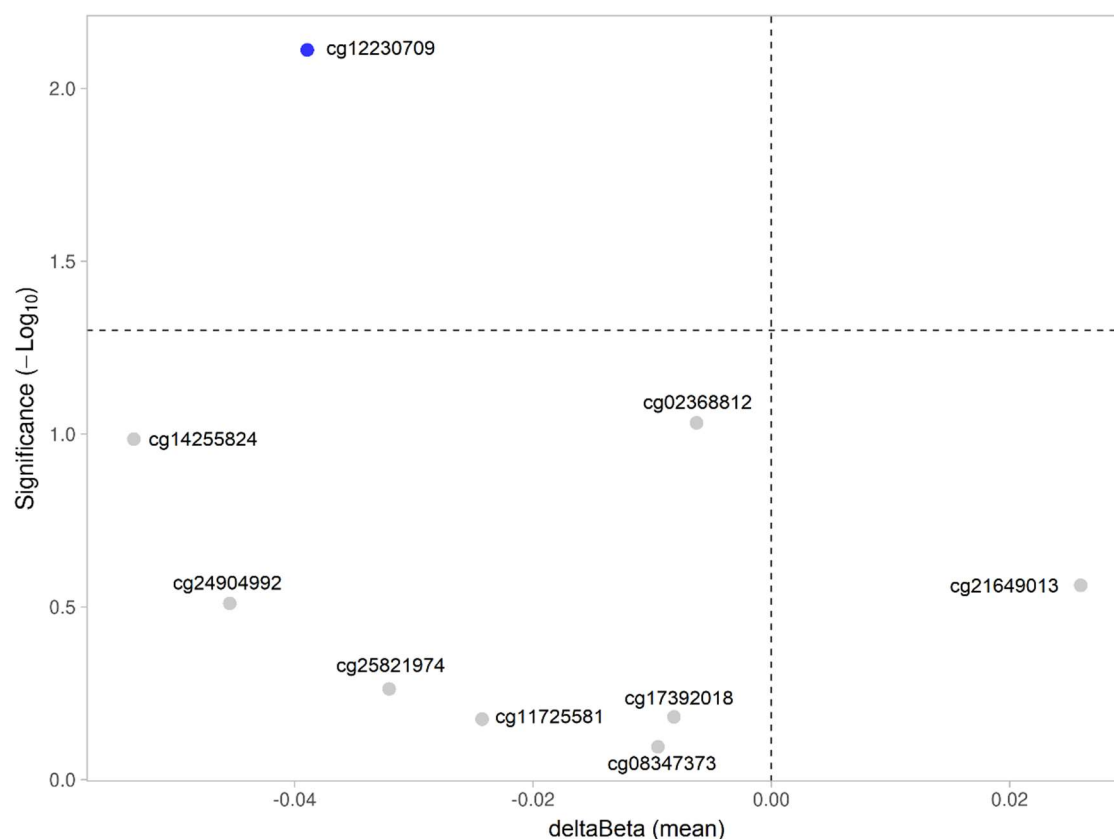
Chr: chromosome; CpG_features: CpG position according to “gene-CpG island”; body: gene body; TSS1500: 1500 nucleotides upstream of transcription start site; 1stExon: CpG located in the first exon of a gene; IGR: intragenic region; 5'UTR located three prime untranslated regions; padj: Benjamini-Hochberg adjusted p-value.

Supplementary information**Supplementary Figure 1: Difference in average beta values between Parkinson's disease patients and healthy controls for each CpG, using DNA derived from blood**

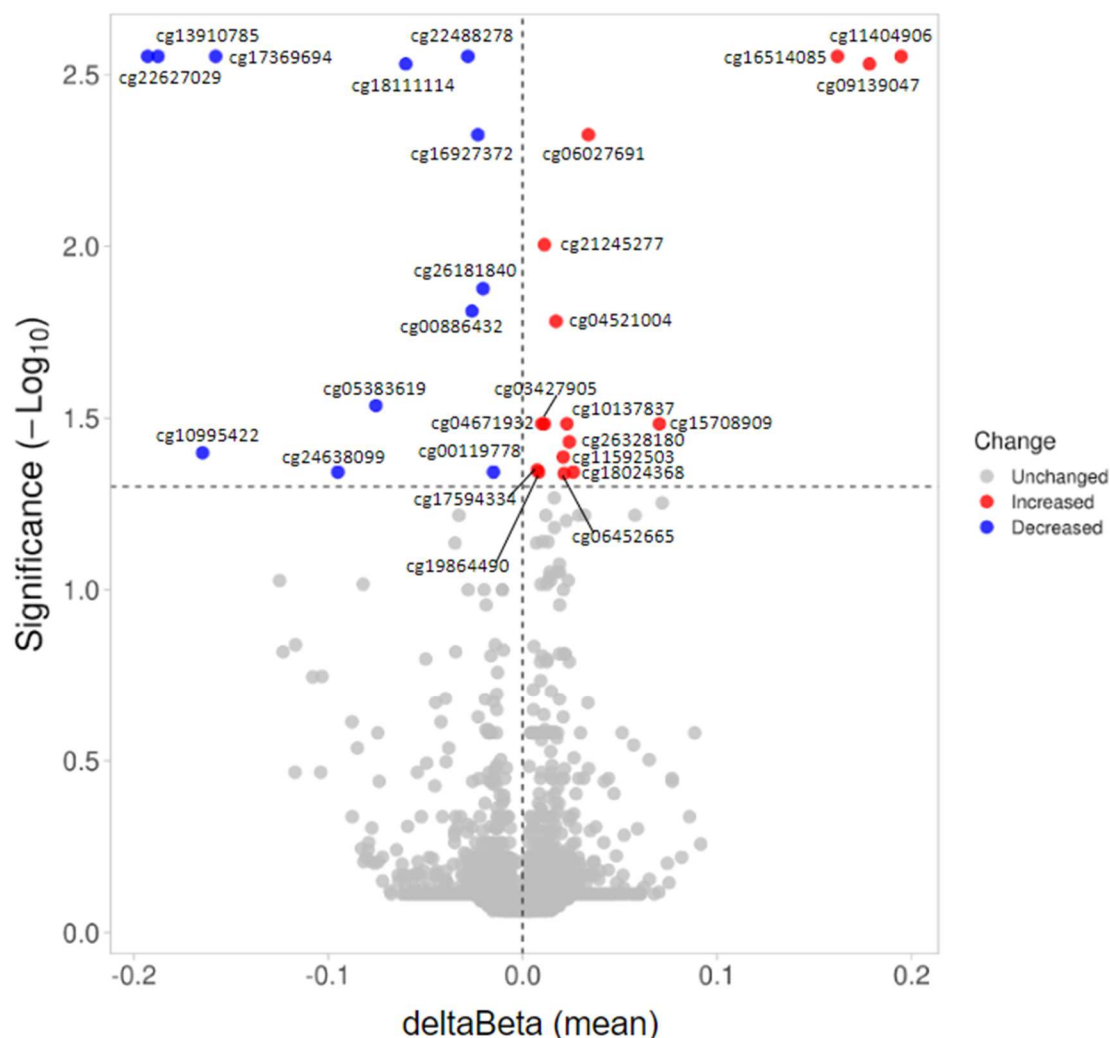
Supplementary Figure 1: Graph showing the distribution of average beta values for each CpG analyzed in DNA derived from blood samples of patients with Parkinson's disease in comparison to healthy controls; p-value after Benjamini-Hochberg correction. Were used n=335 biologically independent samples from patients and n=237 as controls.

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Supplementary Figure 2: Difference in average beta values between Parkinson's disease patients and healthy controls for each CpG, using DNA derived from brain



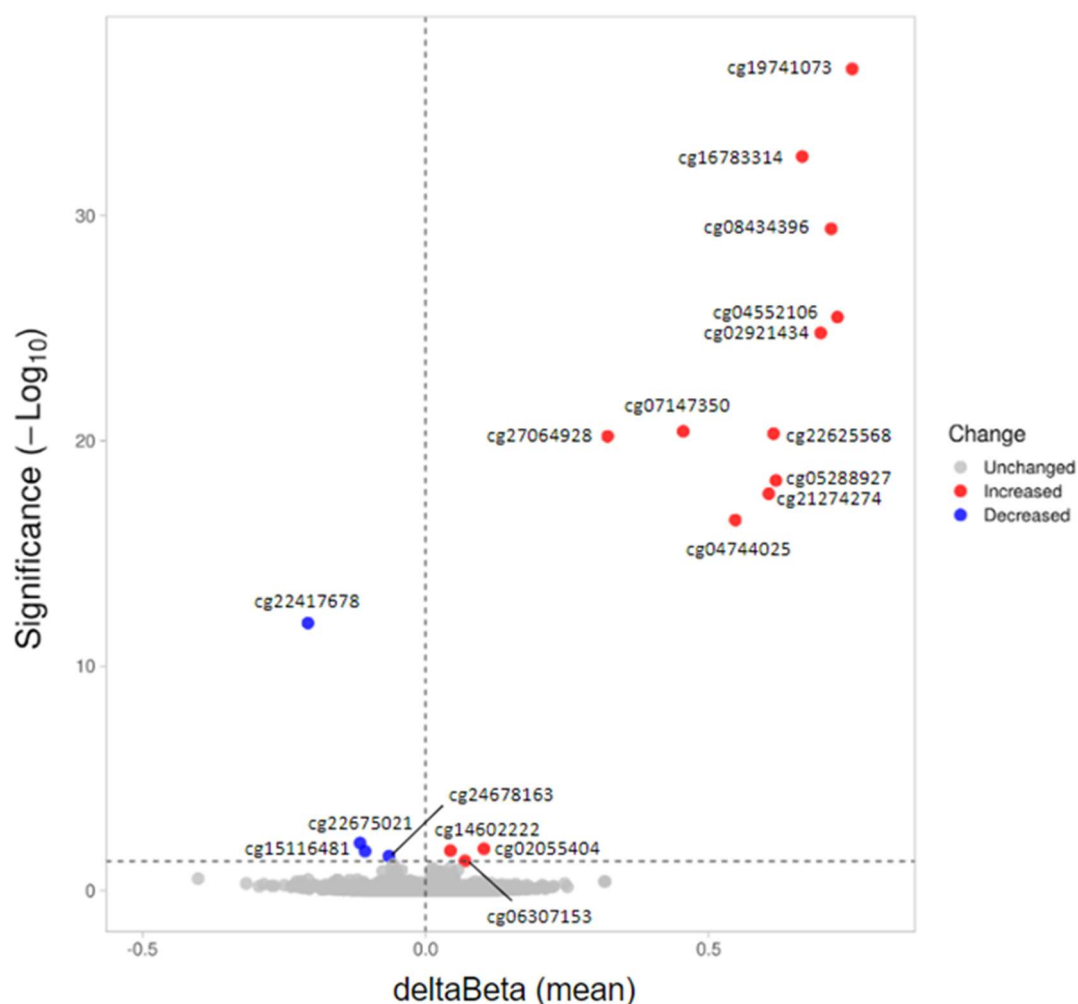
Supplementary Figure 2: Graph showing the distribution of average beta values for each CpG analyzed in DNA derived from brain samples of Parkinson's patients in comparison to healthy controls; p-value after Benjamini-Hochberg correction. Were used $n=38$ biologically independent samples from patients and $n=40$ as controls.

Supplementary information**Supplementary Figure 3: Difference in average beta values between Multiple Sclerosis patients and healthy controls for each CpG, using DNA derived from blood**

Supplementary Figure 3: Graph showing the distribution of average beta values for each CpG analyzed in DNA derived from blood samples of patients with Multiple Sclerosis in comparison to healthy controls; p-value after Benjamini-Hochberg correction. Were used $n=140$ biologically independent samples from patients and $n=139$ as controls.

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Supplementary Figure 4: Difference in average beta values between Fragile X syndrome patients and healthy controls for each CpG, using DNA derived from blood



Supplementary Figure 4: Graph showing the distribution of average beta values for each CpG analyzed in DNA derived from blood samples of patients with Fragile X syndrome in comparison to healthy controls; p-value after Benjamini-Hochberg correction. Were used n=9 biologically independent samples from patients and n=53 as controls.

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Supplementary References

1. Nabais M. F. et al. Meta-analysis of genome-wide DNA methylation identifies shared associations across neurodegenerative disorders. *Genome Biol.* 22, 1, 90; 0.1186/s13059-021-02275-5. (2021)
2. Horvath, S. et al. Huntington's disease accelerates epigenetic aging of human brain and disrupts DNA methylation levels. *Aging.* 8, 7, 1485-1512. 10.18632/aging.101005 (2016).
3. Chuang Y. H. et al. Parkinson's disease is associated with DNA methylation levels in human blood and saliva. *Genome Med.* 9,1, 76; 10.1186/s13073-017-0466-5 (2017).
4. Vishweswaraiah S. et al. Methylated Cytochrome P450 and the Solute Carrier Family of Genes Correlate with Perturbations in Bile Acid Metabolism in Parkinson's Disease. *Front Neurosci.* 16,804261; 10.3389/fnins.2022.804261 (2022).
5. Alisch R.S et al. Genome-wide analysis validates aberrant methylation in fragile X syndrome is specific to the FMR1 locus. *BMC Med Genet.* 14, 18; 10.1186/1471-2350-14-18 (2013).
6. Kular L, Liu Y, Ruhrmann S, Zheleznyakova G et al. DNA methylation as a mediator of HLA-DRB1*15:01 and a protective variant in multiple sclerosis. *Nat Commun.* 9,1,2397; 10.1038/s41467-018-04732-5 (2018).