Epigenetic discordance in young, middle aged and old monozygotic twin pairs

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An ideal model for studying epigenetic changes

Monozygotic twin pairs (MZ twins) have identical genotypes. Yet, they are unique individuals, which may originate through compitition in utero and accumulate during ageing through changes in living conditions. Their differences highlight the importance of the interaction between genotype and the environment, which involves epigenetic regulation. Epigenetic mechanisms regulate the transmittable expression potential of a gene without changing its DNA sequence. Epigenetic changes during the life course are thought to contribute to disease and ageing. In this study we investigate within-pair epigenetic differences in MZ twins over the full adult life range (Table 1).

Conclusions

- Epigenetic discordance can increase considerably at some loci, while other loci remain inert (Figure 1), perhaps due to strong regulation at these loci
- Epigenetic traits can be investigated with an extended version of the classical twin model, that deals with age related changes in variance
- Epigenetic discordance of MZ twin pairs may have a heritable (family environment / genetic) component Figure 4)

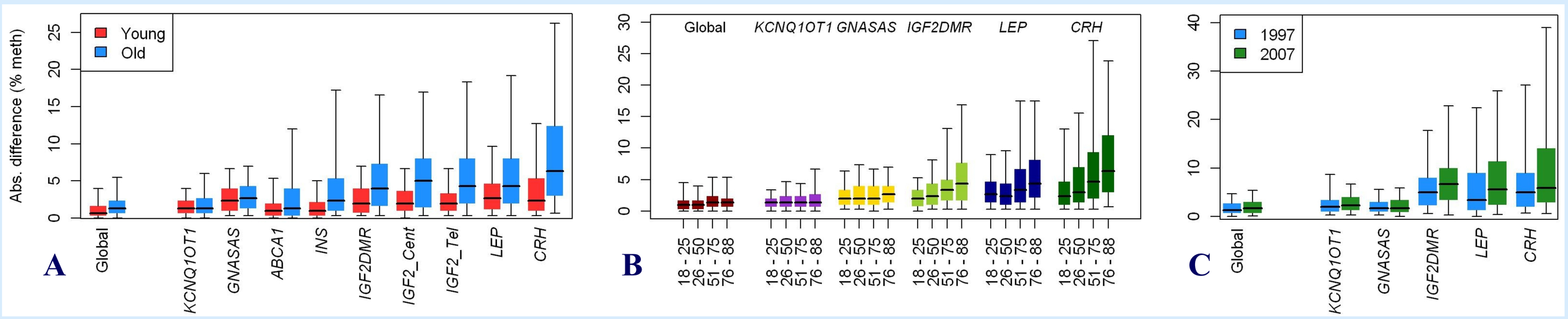

Figure 1: Within pair epigenetic discordance increases with age at some loci

Absolute within pair difference in % DNA methylation for global DNA methylation and for specific loci plotted for **A.** Young NTR MZ twins (red bars) vs. old DTR MZ tins (blue bars). **B.** The full age range, the twin pairs are divided in 4 age categories of equal population size; early adulthood (18 -25 years), young adult to middle aged (26 – 50 years), middle aged to seniority (51 – 75 years), and end of life (76 – 88 years). **C.** The 1997 DNA samples (blue bars) vs the 2007 DNA samples (green bars) of the follow-up DTR MZ twins. The bars show the inter quartile range, the thick line in the center of the bar shows the median and the whiskers show the 5th (bottom whisker) and 95th (top whisker) percentiles.

Table 1: The different MZ twin pair populations investigated in this study

Study / country	Population*	Assays studied	Cell counts#	N (pairs)	Male pairs		Days† (mean / SD)	Same day‡ (pairs)	Age in years mean	Age in years range
Biobank / Netherlands	Young NTR	10	+	66	34		42.8 (126.4)	40	25.2	18.0 – 29.8
	Middle-aged NTR	6	+	61	15		158.3 (286.3)	22	46.3	30.0 – 64.0
	Old NTR	6	+	25	8		116.8 (211.6)	7	70.5	65.0 – 78.0
LSADT / Denmark	Old DTR	10	NA	67	34		29.1 (48.9)	25	79.3	74.1 – 88.0
	Follow-up DTR	6	NA	19	8	1997	32.0 (60.9)	10	76.6	73.2 – 81.8
						2007	10.4 (13.8)	7	86.5	83.4 – 91.8
Total¶	Full adult life span	6	NA	219	91		78.7 (189.5)	94	52.7	18.0 – 88.0

*: The designation for the population sample in this study
#: Availability of data on the amount of the major leukocyte fractions
†: The amount of days between the drawing of blood of both co-twins
‡: The number of twin pairs for whom blood was drawn of both co-twins on the same day
¶: The young, middle-aged and old NTR and the old DTR population samples were combined

Methods

We investigated within pair epigenetic discordance in MZ twins from the Netherlands Twin Register and MZ twins from the Danish Twin Registry., covering the full adult life span (Table 1). Using mass spectrometry we measured the DNA methylation of 9 locus specific assays and an assay that assesses global DNA methylation (Table 2)

We used random effect estimation of linear mixed models to test the increase in variance with age, with an extended version of the classical twin model (white background) where we modeled both the shared or family effect (ai) and the unique or individual effect (ci) around age (yellow background).

Twin pair:

$$Yi1 = \mu + bi + ei1 + ai*agei1 + ci1*agei1$$
$$Yi2 = \mu + bi + ei2 + ai*agei2 + ci2*agei2$$

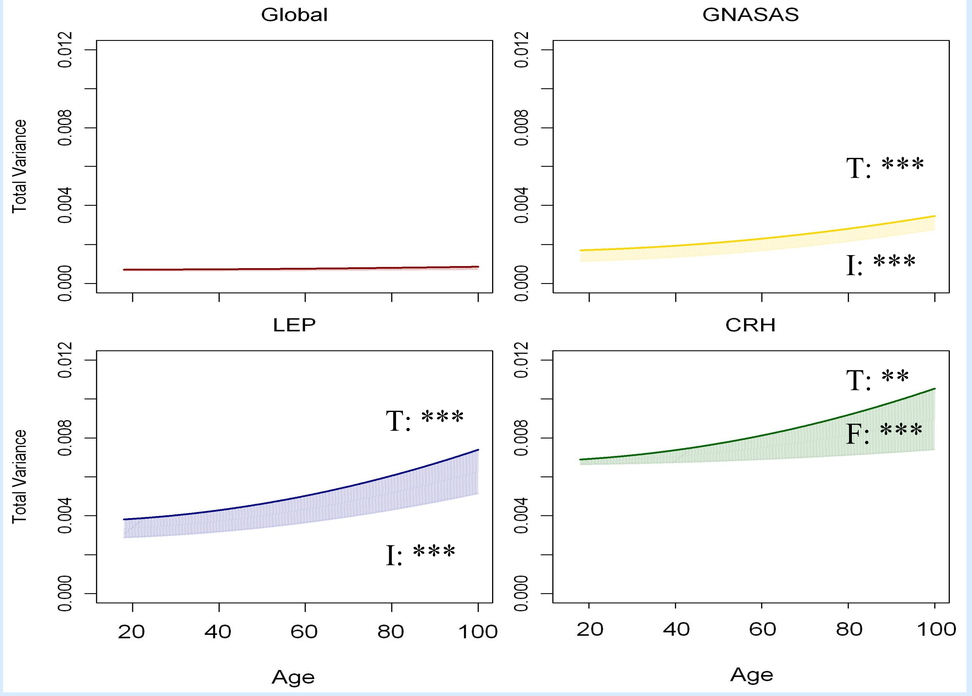

Figure 4: Epigenetic twin discordance with age tested on the extended twin model

The total increase in epigenetic variation (T) with age (thick line) has an individual environment component (I, filled in area under the curve) and a shared (F, family environment / genotype) component (blank area under the curve). *: $p < 0.05$; **: $p < 0.01$; *** $p < 0.001$.

Table 2: The assays and loci measured in this study

Locus	Assay*	CpGs#	Imprinted	Metabolism	All MZ pairs†
ABCA1		4		Y	
LEP		6		Y	Y
CRH		4			Y
IGF2	_DMR	4	Y	Y	Y
	_Tel‡	5	Y	Y	
	_Cent‡	4	Y	Y	
INSIGF		5	Y	Y	
KCNQ1OT1		10	Y	Y	Y
GNASAS		10	Y	Y	Y
LINE1¶		8	Global methylation		Y

*: The name of the assay, if no name it is the same as the locus
#: The number of measured CpG units
†: The assays were measured on all MZ twin populations
‡: Novel methylation assays
¶: Assay developed by Wang et al. AJNC 2010

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