DNA methylation in humans: inter-individual variation and its correlation across 16 Loci

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Introduction

Although epigenetics is frequently proposed to play a role in coronary heart disease (CHD), empirical data are notably sparse. In this project we are, at present, mapping out the inter-individual variation in DNA methylation, which is the best-described layer of epigenetic information and can readily be measured using mass spectrometry on material stored in current biobanks.

To do this we selected 30 out of 4000 individuals from the Netherlands Twin Registry to represent the variation over the properties: sex, age and CVD risk factors using the determinant of the Fisher information matrix (D-optimality). We tested the methylation of DNA extracted from blood of these individuals. We compiled a set of 62 methylation assays, 40 of which could be successfully measured on DNA from blood. On 16 of these assays, we assessed the inter individual variation.

Results and conclusions

1. We found inter individual variation in DNA methylation within and across the 16 loci (see fig. 1).
2. We found that this variation shows a strong positive correlation within and across the imprinted loci (see fig. 2).
3. We found that across the non imprinted loci there appears to be a weaker correlation, both positive and negative, between some (see fig. 2).
4. Next we will test whether this variation is stable during ageing and consistent across tissues. Then we will test for an association with gene expression and phenotype relating to CHD.

Figure 1: Variation in DNA methylation exists both within and across loci

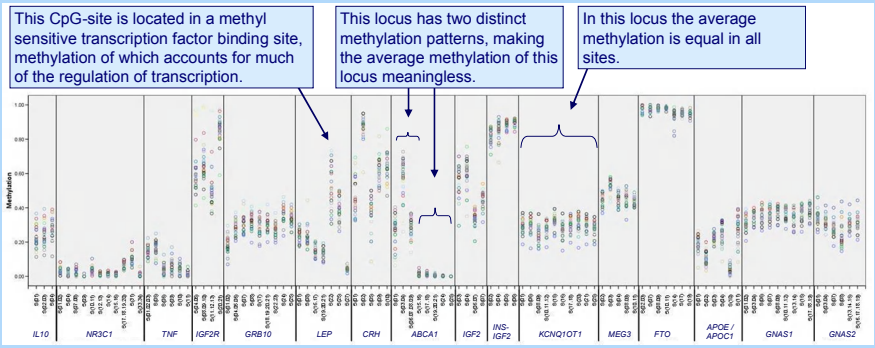
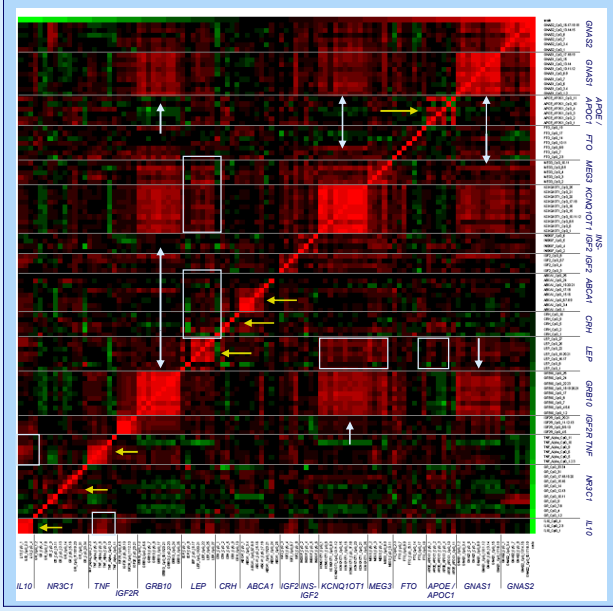


Figure 2: The variation in DNA methylation shows correlation within and across the loci.



- Light blue arrows: the variation in DNA methylation of the imprinted loci shows a strong positive correlation
- Yellow arrows: within the non-imprinted loci the variation also shows correlation, which surprisingly sometimes is negative within a locus (e.g APOE / APOC1,top right)
- Rectangles: some non-imprinted loci appear to show correlation with other loci of their biological pathway (e.g. IL10 and TNF, inflammation)

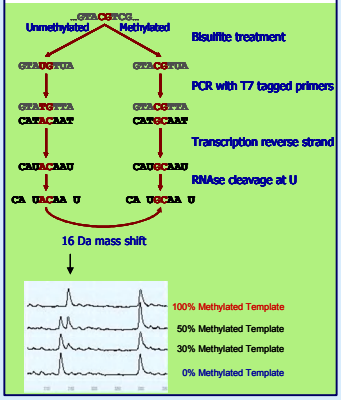
(green: R < 0; red: R > 0)

Additional criteria for selecting the 30 individuals:
- Independent individuals.
- No extreme measurement values.

16 methylation assays selected for their:
- Biological pathway
- Epigenetic properties, such as promoter region, methyl sensitive transcription factor binding sites, imprinting, etc.
- Measurement success rate

Gene / Locus	Involvement in					
	Inflammation	Lipid metabolism	(Fetal) growth	Diabetes	body composition	HPA-axis
IL-10	+					
NR3C1						+
TNF	+			+		
LEP		+			+	
CRH			+			+
ABCA1		+				
FTO				+	+	
APO E / APO C1		+				
IGF2R			+	+	+	
GRB10			+	+	+	
IGF2			+	+	+	
INS-IGF2			+		+	
KCNQ1 OT1			+		+	
MEG3			+		+	
GNAS			+		+	

MassCleave protocol



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