Genome-scale DNA methylation analysis of melanocytic nevi: mechanisms driving stability

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BACKGROUND

- **Acquired melanocytic nevi (AMN)** are nearly all stable, but share cutaneous and molecular characteristics with melanoma and may rarely transform.
- **Histopathological classification** of AMNs is based on the location and proliferation of melanocytic nests (junctional, intradermal, compound) and generally consists of 'benign' or 'dysplastic' classes.
- **Dermoscopic classification** is used for clinical decision-making, and consists of phenotypic description of lesions (globular, reticular, non-specific).
- Evidence for which of these combinations of classes and patterns of AMNs carry higher risk for transformation is lacking, and **mechanisms driving stability of most AMNs are yet unclear.**

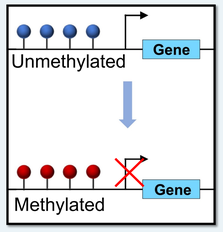


Figure 1. DNA methylation plays a critical role in the regulation of gene expression, for example at gene promoters by inhibiting transcription.

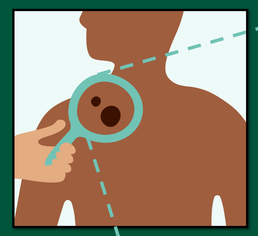
METHODS

- Methylation-profiling of **32 AMNs** and **32 adjacent normal skin** samples from **24 patients** using **Illumina EPIC array**.

Table 1. Nevi Characteristics

Variable	Subjects (N = 24)	Samples (N = 32)
Sex N (%)		
Female	7 (29.2)	
Male	17 (70.8)	
Age mean (SD)	51.88 (14.36)	
Status N (%)		
Benign		13 (40.6)
Dysplastic		19 (59.4)
Histopath N (%)		
Compound		13 (40.6)
Intradermal		12 (37.5)
Junctional		7 (21.9)
Dermoscopic Pattern N (%)		
Globular		10 (31.2)
Reticular		4 (12.5)
Non-specific (PRG)		10 (31.2)
Non-specific (other)		8 (25.0)
Sun Exposure N (%)		
Exposed		25 (78.1)
Shielded		7 (21.9)
BRAF N (%)		
BRAF V600E		25 (78.1)
BRAF V600K		3 (9.4)
BRAF V600R 1(3)		1 (3.1)
NRAS G12S 1(3)		1 (3.1)
unknown		2 (6.3)

Key Points



Methylation profiles of 32 acquired melanocytic nevi

- 100% *BRAF* or *NRAS* mutation
- Estimation of nevus cell-type composition
- **Benign Nevi** (vs. Dysplastic):
  - Tend to be globular (69%) or non-specific (31%)
  - Increased inferred melanocyte proportion
  - Similar methylation profile to adjacent normal skin
  - Increased global methylation
  - Increased Alu/LINE-1 methylation
- **Dysplastic Nevi** (vs. Normal Skin):
  - Tend to be reticular/non-specific (95%)
  - Distinct from adjacent normal skin
  - Increased global methylation in actively transcribed regions
  - Decreased global methylation in enhancer elements
- **Globular Nevi**:
  - Similar methylation profile to normal skin
- **Non-Globular Nevi** (Reticular/Non-Specific):
  - Strongly distinct from normal skin
  - Increased global methylation in actively transcribed regions
  - Decreased global methylation in enhancer elements
  - **Strong methylation of tumor suppressor *PTEN* promoter**

SCAN ME

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RESULTS

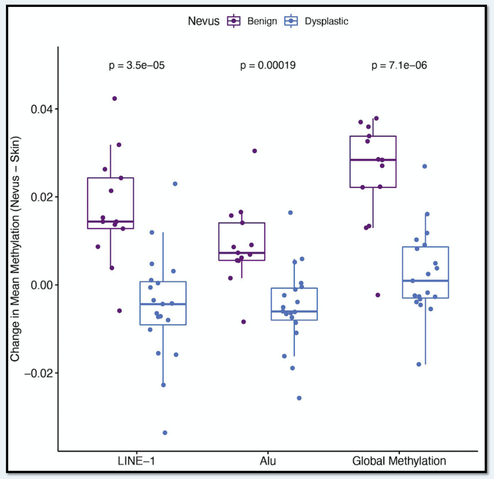

Figure 2. Benign AMNs have increased genomic stability vs. dysplastic AMNs via increased methylation of LINE-1 and Alu retrotransposons and global methylation.

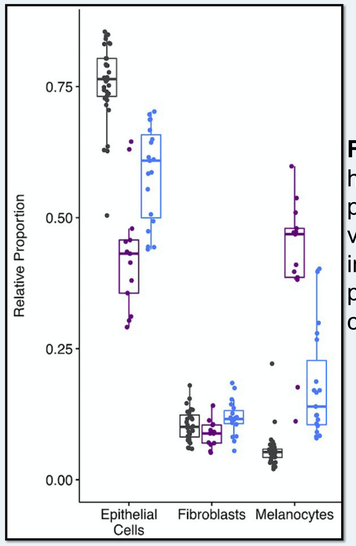

Figure 3. Benign AMNs have an increased proportion of melanocytes vs. dysplastic AMNs, inferred from methylation-profile estimation of AMN cell type composition.

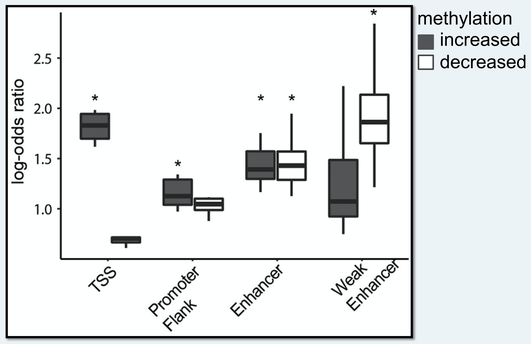

Figure 4. Non-globular AMNs (reticular/non-specific) have global increases in methylation at promoters and decreases in methylation at enhancer regions.