

1.5 Regulation of gene expression

Name: _____ Class: _____ Date: _____ **Total: 23 marks**

KEY WORDS enhancer

Objective

Reason about enhancers, combinatorial specificity and epigenetic modification of disease.

1 Key knowledge and worked examples

■ **Specificity is combinatorial**

A 6-base motif occurs every $4^6 = 4096$ bp – ~1.6 M times per strand; only combinations of factors cut false hits multiplicatively ✓. Enhancers act by looping, orientation-independent, from up to 100 kb.

■ **Worked example: one upstream base**

Lactase persistence: one base 14 kb upstream strengthens an enhancer → LCT stays on into adulthood – a zero-protein-change trait ✓.

2 Practice

2.1 How often does a random 8-base motif occur per strand (6.4×10^9 bp)? [3]

2.2 Distinguish promoter from enhancer in one sentence each. [3]

2.3 Why is “epigenetic” not “permanent”? [3]

3 Exam-style questions

3.1 A transcription factor binds a 6-base motif.

Compute the expected genome-wide hit count. Explain why cooperating factors binding adjacent sites restore specificity, quantitatively. State one consequence for interpreting non-coding disease variants. [7]

3.2 Fictional monozygotic twins, same variant, different severity; one has promoter methylation silencing that allele.

Explain why sequence identity does not guarantee phenotype identity. State what methylation (70–80 % of CpG) does to enhancer/promoter access. Explain why methylation assays sit next to sequencers diagnostically. [7]

Solutions

2.1

- $6.4 \times 10^9 / 4^8 = 6.4 \times 10^9 / 65\,536 \approx 98\,000 \checkmark$.

2.2

- Promoter: fixed position at the transcription start, assembles Pol II. Enhancer: distance- and orientation-independent, boosts via looping.

2.3

- Marks are copied through cell divisions but are reprogrammable (development, some therapies target writers/erasers).

3.1

- $6.4 \times 10^9 / 4096 \approx 1.6 \times 10^6 \checkmark$.
- Two cooperating 6-base sites: expected joint hits divide by ~ 4096 again $\rightarrow \sim 380$ – specificity returns multiplicatively.
- Consequence: most disease-relevant non-coding variants sit in regulatory logic, not code.

3.2

- Access differs: methylation compacts chromatin, silencing the allele without changing letters.
- Methylated CpG recruits repressors/compact histone marks $\rightarrow$ enhancer and promoter inaccessible.
- Diagnostics: severity modifiers live in the access layer, so assays of methylation complement sequencing.