I. Classification of mutations

point mutation = single base pair change
- **transition** = purine to purine or pyrimidine to pyrimidine
- **transversion** = purine to pyrimidine or pyrimidine to purine

insertions & deletions are most common in **microsatellites** (1-4 bp sequence repeated a variable number of times)

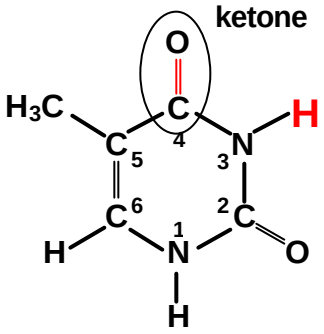
chromosome rearrangements (translocation, inversion, deletion)

loss of function – usually recessive (remaining allele still has function)
- **null** or **amorphic** = complete loss of function
- **leaky** or **hypomorphic** or **weak** = partial loss of function

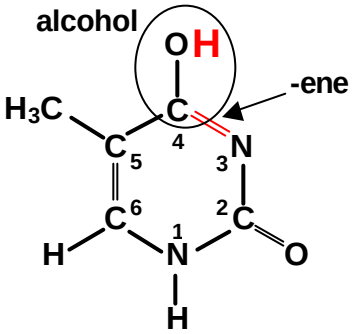
gain of function – often dominant
- **germline** = occurs in cells giving rise to eggs and sperm; heritable
- **somatic** = occurs in the body; not heritable, but can have other effects (*e.g.* cancer)

II. Spontaneous sources of mutation

tautomeric shifts – movement of a hydrogen and the corresponding bond



thymine (keto)



thymine (enol)

T is usually in the **keto** form, but can occasionally shift to the **enol** form; T in the enol form pairs with G. Likewise, G can shift to the enol to pair with T.

C is usually in the **amino** ($C–NH_2$) form, but can shift to the **imino** (C=NH) form; C in the imono form pairs with A. Likewise, A can shift to imino to pair with C.

Spontaneous tautomeric shifts during replication can cause mispairing, and eventually a transition mutation. (Mispairing due to ionization of bases is now thought to be more common, but Griffiths doesn't really cover this, so we won't.)

depurination – spontaneous breakage of the nucleoside linkage in purines generates an **apurinic** (**AP**) site; occurs about 10,000 times per human cell per day; during replication, polymerase doesn't know what nucleotide to put opposite an AP site.

deamination of cytosine converts it to uracil; if not removed, it will pair with A next replication, leading to a C/G to T/A transition.

Most small insertions and deletions occur in **microsatellite** sequences: repeats of very short sequences (1-4 bp). The Streisinger model postulates strand slippage during replication.

Unequal crossing over between repeats can also alter repeat number. A number of human disease are associated with expansion of triplet repeats. The higher the number of repeats, the more unstable is the tract.

Attempts to replicate past DNA damage can cause more severe problems than the original damage. Unwinding a replication fork past a single-strand nick converts it into a double-strand break; this is probably the biggest source of double-strand breaks. Sometimes replication blocks are bypassed by special **bypass polymerases**, which are error-prone. For example, Pol η (eta) inserts AA across from pyrimidine dimers. About 75% of pyrimidine dimers are TT, but that means Pol η is wrong 25% of the time.

Reactive oxygen species can damage bases. The aerobic environment in the cell produces reactive oxygen species, including hydrogen peroxide (H_2O_2) and oxygen free radicals ($^{\cdot}OH^{-}$). These can modify bases to create thymine glycol, which blocks replication, or 8-oxo-G, which frequently mispairs with T.

Transposable elements can insert into genes, cause chromosome breakage after excision (DNA IR elements), or cause chromosome rearrangements due to recombination between dispersed copies (TEs are discussed more a few lectures from now).

III. Induced mutation and mutagens

mutagen is any agent that causes changes to DNA

base analogs are chemicals that mimic normal bases, but may base-pair differently

base modifying agents alter bases so they base-pair differently during replication; require two rounds of replication for change to become fixed in the genome

intercalating agents – insert between stacked bases; mess with replication to result in insertion or deletion of base pairs from the normal sequence

ultraviolet radiation (UV light) causes primarily cyclobutane **pyrimidine dimers** and 6-4 photoproducts, which block transcription and interfere with replication.

ionizing radiation (X rays, gamma rays, cosmic rays) generates reactive oxygen species and free radicals, which can alter bases and break sugar-phosphate backbones. Double-strand breaks can lead to chromosome rearrangments.

crosslinking agents create covalent bonds between bases on opposite strands, a type of damage that is very difficult to repair; some chemotherapy agents are crosslinkers.