I. Following are the results of reversion tests and pairwise crosses between a series of 8 rII mutants of Phage T4. + in the reversion tests means revertants were detected while + in the cross results indicates significantly higher frequency of recombinants over the reversion rate and – indicates background reversion only, when applicable.

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Reversion</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
<th>M7</th>
<th>M8</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M2</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>M4</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M6</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M7</td>
<td>+</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M8</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

A. Which rII mutants are point mutations? M1, 2, 4, 7, 8
Deletions? M3, 5, 6

B. Make a map of the RII A region that involves these mutants. Show relative locations of each.

\[ \begin{align*}
\text{M5 del} & \text{ M8} \\
\text{M3 del} & \text{M7} \\
\text{M6 del} & \text{M1} \\
\text{M4 del} & \text{M2}
\end{align*} \]

C. How were the crosses made and progeny scored? Crosses were made on E. coli B and the progeny plated on lawns of E. coli K (The rII mutants do not reproduce on K, only rII+)

II. A cross was made in the fungus Sordaria, between parents that were, un, cyh and un+, cyh+ and 100 linear tetrads were isolated. There proved to be six classes in the following proportions:

<table>
<thead>
<tr>
<th>TT</th>
<th>TT</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{un} \cdot \text{cyh}</td>
<td>\text{un} \cdot \text{cyh}</td>
<td>\text{un} \cdot \text{cyh}</td>
</tr>
<tr>
<td>\text{un}^+ \cdot \text{cyh}</td>
<td>\text{un} \cdot \text{cyh}^+</td>
<td>\text{un} \cdot \text{cyh}</td>
</tr>
<tr>
<td>\text{un} \cdot \text{cyh}^+</td>
<td>\text{un}^+ \cdot \text{cyh}</td>
<td>\text{un}^+ \cdot \text{cyh}^+</td>
</tr>
<tr>
<td>15</td>
<td>29</td>
<td>47</td>
</tr>
</tbody>
</table>

\text{PD} \text{ NPD} \text{ TT}

Are the genes linked? Yes

\text{f(PD)} \gg \text{f(NPD)}
III. (from: Blood 98: 248-250) Two unaffected first cousins married and had a son who has a serious case of Von Willebrand Disease (VWD), an autosomal recessive condition that prevents blood clotting. Sequence analysis showed that the boy was homozygous for an unusual allele also found in both parents, in which 5 base changes found over a 200 base sequence in exon 28 (there are 52) are the same as are found in a pseudogene that is also present in both parents. One of the base changes creates a nonsense codon. All the remaining sequences including the other 51 exons in this allele show no coding differences from the normal allele.

A) Suggest a mechanism for the origin of the unusual allele that seems to have originated from one of the common grandparents of the affected boy. Explain your rationale.

Gene conversion following mis-pairing of a normal allele with the segment of exon 28 present in the pseudogene. Rationale: this could explain multiple changes in one short region easier than other models.

B) What is the F value for the boy? (first cousins have one set of common grandparents) (show the path diagram)

\[
F^+ (1/2)^5 + (1/2)^5 = 1/16
\]

C) A mild form of the same disease is common in Doberman pinschers, which like many dog breeds are relatively inbred populations. In fact about 36% of registered Dobermans have the mild disorder.

1) Propose an explanation why the disease is common in this breed but rare overall.

Founder effect followed by inbreeding

2. Estimate the allele frequencies and the genotypic distribution in this breed.

\[
q = f(vwd) = \sqrt{0.36} = 0.6, \text{ so } p = F(VWD) = 0.4
\]

with random mating would expect 16 VV : 48 Vv : 36 vv

3. If a breeder with a Doberman dog colony with the distribution above decides to neuter any affected pups so they will not pass on the allele, (a) what will happen to the gene frequency after one generation of random mating among the remaining dogs?

if the 36 vv are neutered, the F(V) becomes \((2 \times 16 + 1 \times 48)/(2 \times 16 + 2 \times 48) = 0.625\) and q=0.375; Random mating would give 39 VV : 47 Vv : 14 vv

(b) After 2? eliminating the 14 from the breeding population would give \(p = 0.727\) and \(q = 0.273\)

(c) What would be the effect on the population if the selection was halted after 2 generations of selection. In the absence of forces, the colony would stabilize at these allele frequencies, so that only 7.45% would have Von Willebrand disease.

4. A DNA–based test is now available ($140) that can identify the presence of the defective allele. How many generations would it take to eliminate the allele if all dogs in the colony that test positive are prevented from breeding. Only one generation would eliminate all v alleles (until a new mutation came along)
IV. Barth Syndrome, Navajo Neuropathy and Leigh Syndrome all have neuropathologic symptoms including motor impairment, muscle weakness, and in some cases cardiac failure. All are rare and show simple but different patterns of inheritance.

Below are pedigrees (idealized!) for each of the diseases: A) Suggest the mode of inheritance of each: (remember that 3 different modes are involved!)

B) Propose an explanation as to why the 3 diseases have similar phenotypic effects.

All show symptoms associated with lack of ATP, a mitochondrial function and since many of the associated enzymes have both nuclear and organelle encoded subunits, this seems a logical explanation.

C) Could maternal effect explain any of the pedigrees? Explain

Yes, there is nothing in the Leigh pedigree that would eliminate a maternal protein in the egg causing the phenotype. That would be confirmed as a possibility if an affected daughters did not pass the trait on to the next generation, but we do not see that in this pedigree.
IV. A homozygous recessive (aa) maize plant is crossed to a plant that is trisomic for chromosome 10. This plant is homozygous (2 or 3 copies) for the dominant A allele. F1 progeny all show the dominant phenotype. One F1 plant that is identified via root tip chromosomes as being trisomic for chromosome 10 is crossed back to the aa mutant parent.

A) What ratio will be expected if the A gene locus is not on chromosome 10?
   In that case the backcross would be Aa by aa so the ration would be 1 As: 1 aa

B) If the A locus is on chromosome 10 and the F1 is used as the male where only 1N pollen is functional, what ratio will be expected in the backcross progeny.
   - The F1 trisomic would be AAa so the viable pollen would occur in the ratio 2(A) : 1 (a), giving 2Aa: 1aa in the progeny

C) If the A locus is on chromosome 10 and the F1 is used as the female where disomic eggs are functional, what ratio will be expected in the backcross progeny.
   - Here the female gametes would occur in the ratio: 2(A) : 2 (Aa) : 1(AA) :1 (a), so 1 in 6 progeny of the cross to an aa would have the recessive phenotype.

D) What fraction of the progeny would show the mutant phenotype if this F1 plant is self fertilized and the conditions in B and C still apply?
   - Eggs: 2(A) : 2 (Aa) : 1(AA) : 1 (a)
   - Pollen: 2(A) 4AA : 4 AAa : 2 AAA : 2Aa
     1(a) 2 Aa : 2Aaa : 1AAA : 1 Aa or 1 in 18 shows the recessive phenotype

V. Achondroplasia (a form of dwarfism) is a dominant single gene trait that is lethal (prenatal) when homozygous. On the average, one baby in 25,000 is born with the condition.

A) Estimate the gene frequency for the Ach and ach alleles. All affected are Ach/ach so the F(Ach) = 1/50,000 alleles (0.00002) and F(ach) is 0.99998

B) Assuming a population of 100,000, and given that the homozygous Ach/Ach condition is lethal, and that the fitness of the dwarf heterozygotes is 0.25, what would be expected to happen to the frequency of the Ach allele in the next generation?
   - Only 1 of the 4 Ach’s would be represented in the next generation (s=0.75), and since selection is against a dominant allele the frequency should drop rapidly

C) Observations show the frequency of achondroplastic dwarf births remains consistent at 1 in 25,000. How can this be explained? There must be a high mutation rate of 3/100,000 gametes
VI. 1) The chromosome maps for 3 chromosomes for 3 inbred mouse colonies are shown below. Within each colony, the mice are homozygous for the arrangements shown.

<table>
<thead>
<tr>
<th>Chrom.</th>
<th>Colony 1</th>
<th>Colony 2</th>
<th>Colony 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 2 • 3 4 5 6 7</td>
<td>1 2 3 6 5 4 7</td>
<td>1 2 3 4 5 G H</td>
</tr>
<tr>
<td>2</td>
<td>A B C D • E F G H</td>
<td>A B C D • E F G H</td>
<td>A B C D • E F 6 7</td>
</tr>
<tr>
<td>3</td>
<td>L M N O P • Q</td>
<td>L M M N O P • Q</td>
<td>L M N O P • Q</td>
</tr>
</tbody>
</table>

Show how the chromosomes would pair in hybrids between mouse colony 1 and 2, 1 and 3 and 2 and 3; Name any aberrations present, and predict the relative fertility in males for each combination.

1 X 2 reciprocal translocation in Ch 1 and a duplication in Ch2. The large inversion predicts 50% fertility in a male

1 X 3 reciprocal translocation TL 1-2; 50% sterility in males due to adjacent segregation

2 X 3 reciprocal translocation with a broken up inversion for Chs 1 and 2 and a duplication on Ch3, the two factors should reduce male fertility to 25%

the figure showing gene for gene pairing is too complex for me to draw on my computer.
VII. A) Rabbits from one true breeding herd have 6 cm average ear length (Var = 1) while those from another have and average ear length of 4 cm (Var = 0.8). The average for the F1 progeny from crossing animals from these two colonies is 5 cm ears (Var = 1.2). F2 progeny from sib matings also average 5 cm ears (Var = 4), but the range is from 2 cm to 8 cm. Out of 100 total F2 progeny only 1 had 2 cm ears and 2 had 8 cm ears.

1. Calculate heritability based on the information given. Is it H² or h²?
   \[ V_t \text{ from the F2 is 4, the average } V_e \text{ from the parents and F1 is one, so } V_g = 3 \text{ and } H^2 = \frac{3}{4} \]

2. How many genes are heterozygous in the F1? 1 or 2 from 100 progeny is closest to \((\frac{1}{4})^3\) so there are 3 genes and \(N = 3\); 4 genes would give only 1 in 256

3. What fraction of the F2 progeny will have 5 cm ears? What fraction of these will be true breeding?
   Since the F2 range is 2 (no contributing alleles) to 8 (6 contributing alleles) each “prime” adds 1 cm. Thus 5 cm means 3 contributing alleles and
   \[ \frac{6!}{3! \cdot 3!} \cdot \left(\frac{1}{2}\right)^3 \cdot \left(\frac{1}{2}\right)^3 \text{ or } \frac{5}{16}. \] Since none can be homozygous, none will breed true.

Give possible genotypes for the two true breeding parents.
4 cm  A‘A’, BB, CC X 6 cm AA, B’B’, C’C’

B) h² for egg weight in a flock of white leghorn chickens if 0.6. If a breeder keeps back only large eggs for hatching that on the average are 10 gm heavier than the overall average weight, what can he expect to happen to the average egg weight in the next generation? What will happen if he keeps following the same procedure for many generations?

The eggs should average 6 gm more in the next generation; the average weight would continue to rise with selection, but the h² would decrease as more contributing alleles accumulated, so progress would slow down. It is very likely that egg-weight gains would be offset by a loss in number or some other “cost”.

VIII. A transposon recovered from a fish genome has been found useful as a tool in both gene identification and gene delivery in mammals, including humans (tissue culture at this point). The Tn is called “Sleeping Beauty” (SB) since it seems to have been inactive in the original host for centuries.

A) Propose an explanation as to why it is no longer active in the fish host but becomes active when transformed into a new host.
   The multiple copies in the fish host led to silencing via methylation, or as in the P elements, a faulty Ts’ase that bound the ends preventing movement

B) Predict key features of the SB Tn. Inverted terminal repeats recognized by an active Transposase/integrase gene copy.

C. How might SB used for gene delivery? Insert a gene of interest with a promoter “inside” the Tn; if the Ts’ase is disrupted, it will be necessary to cotransform with a functional copy

D) How could SB be useful in determining normal gene function?
   The Tn will insert into and knock out host genes, thus also “tagging them: it can also be used and in C to deliver genes for testing complementation of defective genes.
IX. List features, with explanations, that make *C. elegans* especially useful for studies of development.

AMONG OTHERS:
- they can self and cross to produce many progeny
- the life cycle, egg to egg requires only 3 days
- they are transparent so every cell can be seen
- they have only around 1,000 cells and the developmental fate of each cell is known
- RNAi is easily used to turn off any gene
- laser ablation allows destruction of any specific cell
- small sequenced genome helps identify genes
- mutants available.