Both John and Karen are deaf due to genetics. Why then could they have only normal children?
Genetic analyses of a variety of plants and animals have revealed that many phenotypes are the result of gene interactions.

**Gene interactions:** the collaborative efforts of two or more genes in specifying the phenotype for a specific trait.

Jargon:
- complementary gene action and genetic heterogeneity
- additive gene action
- epistatic gene interaction
- modifier and suppressor
A mutant gibberellin-synthesis gene in rice
New insight into the rice variant that helped to avert famine over thirty years ago.
Nature 416: 701  April 18, 2002

The chronic food shortage that was feared after the rapid expansion of the world population in the 1960s was averted largely by the development of a high-yielding semi-dwarf variety of rice known as IR8, the so-called rice ‘green revolution’. The short stature of IR8 is due to a mutation in the plant’s sd1 gene, and here we identify this gene as encoding an oxidase enzyme involved in the biosynthesis of gibberellin, a plant growth hormone.

Gibberellin is also implicated in green-revolution varieties of wheat, but the reduced height of those crops is conferred by defects in the hormone’s signalling pathway. There are various reasons for the dwarf phenotype in plants, but gibberellin (GA) is one of the most important determinants of plant height. To investigate whether the sd1 gene in semi-dwarf rice (Fig. 1a) could be associated with malfunction of gibberellin, we tested the response of this mutant to the hormone. We found that sd1 seedlings are able to respond to exogenous gibberellin, which increases their height to that of wild-type plants.

In the early 1970s, a Dr. Rutger, then in Davis, Calif., fired gamma rays at rice. He and his colleagues found a semi-dwarf mutant that gave much higher yields, partly because it produced more grain. Its short size also meant it fell over less often, reducing spoilage. Known as Calrose 76, it was released publicly in 1976. Today, Dr. Rutger said, about half the rice grown in California derives from this dwarf.

Right: wild-type
Left: semi-dwarf (sd1) mutant (more resistant than wild-type to damage by wind and rain and respond better to certain fertilizers)
Arabidopsis dwarf mutants: untreated (right) and treated with an application of gibberellin (left)

These plants have the same genotype--they are homozygous for the same recessive, loss-of-function mutation.

Consider the following situation: you have three different (independently isolated) dwarf strains of Arabidopsis.

• Treatment of each mutant strain with gibberellic acid restores normal phenotype for mutant 1, 2 and 3 suggesting that they have the same primary defect.
• You cross mutant 1 X 3 and the untreated F1 are dwarf.
• But when you cross 1 X 2 the untreated F1 are wild-type.
• How to explain: dwarf X dwarf = wild-type?
Look at gibberellin biosynthetic pathway

Gibberellin is made via the mevalonic acid pathway.

\[ \text{Mevalonic acid} \rightarrow \text{Isopentenyl pyrophosphate} \]

\[ 4 \text{ isopentenyl pyrophosphates} \xrightarrow{\text{enzyme A}} \text{Geranylgeranyl pyrophosphate} \]

\[ \xrightarrow{\text{gene A}} \text{Gene A} \]

\[ \xrightarrow{\text{enzyme B}} \text{Gene B} \]

\[ \text{Kaurenol} \xrightarrow{\text{enzyme C}} \text{Gene C} \]

\[ \text{Other gibberel} \]

\[ \text{GA}_12 \text{ aldehyde} \xrightarrow{\text{stimulates plant growth}} \]

Dwarf plants an example of \textit{genetic heterogeneity}.
Genetic (or locus) heterogeneity:
Mutations in any one of several genes may result in identical phenotypes (such as when the genes are required for a common biochemical pathway or cellular structure)

Heterogeneous trait or genetic heterogeneity
a mutation at any one of a number of genes can give rise to the same phenotype

Although a single gene difference causes the phenotypic difference between the dwarf and the wild-type plants, this does not mean that normal height is the result of the action of a single gene. It means simply that only one gene differed* between the dwarf and wildtype plants under consideration

* carried alleles with functional differences
These mutations show complementation:

**Complementation**: the production of wild-type F1 progeny when crossing two parents showing the same recessive mutant phenotype

M1 X M2 → wild-type F1 progeny

Look at genotypes
(alleles symbols: uppercase = functional allele; lowercase = loss-of-function):

mutant 1: aaBBCC X mutant 2: AAbbCC

F1      AaBbCC    wild-type

↓  self

What phenotypes will appear in the F2?
Will the progeny ratios be in 1/4’s or 1/16’s or 1/64’s
Genes are assorting independently

\[
\begin{array}{ccc}
3/4 & A- & 1/4 & aa \\
3/4 & B- & 1/4 & bb \\
\end{array}
\]

all CC (not segregating)

\[
\begin{array}{ccc}
9/16 & A-B- & CC \\
3/16 & aaB- & CC \\
3/16 & A- & bb & CC \\
1/16 & aabb & CC \\
\end{array}
\]

*Since a homozygous recessive mutation in either A or B results in the mutant phenotype*

\[
\begin{array}{ccc}
9/16 & \text{wild-type} \\
7/16 & \text{dwarf} \\
\end{array}
\]
Example: Short-winged fly
• You have three mutant strains of fruit fly.
• All strains have short wings.
• Are they mutated in the same gene or different genes?
• Are any of these new mutations alleles of the vestigial gene located on chromosome #2?

How would you answer these questions?
**Complementation Test**
A complementation test is commonly used to define functional units (genes) for *recessive* mutations that result in the same phenotype

\[ M1 \times M2 \rightarrow \]
\[ F1 \text{ mutant phenotype (short wings)} \]
These mutations fail to complement and are alleles of the same gene

\[ M1 \times M3 \rightarrow \]
\[ F1 \text{ wild-type phenotype (long wings)} \]
These mutations complement and are alleles of different genes

\[ M3 \times vestigial \rightarrow \]
\[ F1 \text{ mutant phenotype (short wings)} \]
These mutations fail to complement and are alleles of the same gene
write out genotypes for the above crosses
a+ = wild-type allele of gene a
a' = recessive mutant allele of gene a
a^2 = another recessive mutant allele of gene a
vg+ = wild-type allele of the vestigial gene
vg = recessive mutant allele of the vestigial gene

**M1 genotype**  \( a'^1a'^1vg^+vg^+ \)

**M2 genotype**  \( a'^2a'^2vg^+vg^+ \)

**M3 genotype**  \( a'^1a'^1vg \ vg \)
(\textit{mutation in the vestigial gene})