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Dr. Momiao Xiong
Professor
The University of Texas Health Science
Center at Houston

Biography

- Momiao Xiong, Ph. D, Professor in Division of Biostatistics and Human Genetics Center, University of Texas School of Public Health. Dr. Xiong graduated from the Department of Statistics at the University of Georgia in 1993. From 1993 to 1995, Dr. Xiong was postdoctoral fellow at the University of Southern California working with Michael Waterman.

Summary of Research Interests

- Statistical genetics
- Population genetics
- Computational systems biology
- Bioinformatics

Population Genetics

- Unlike Mendel, Charles Darwin made a big splash when his defining work, "On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life" (which we refer to as "The Origin of Species") published in 1859.
- Darwin set forth a scientific theory that described how one species could give rise to another species, given sufficient time. It was heavily attacked at the time (and continuing to this day) by people who thought that it contradicted their religious beliefs. Nevertheless, the basic theory has survived and flourished, and today it is one of the main pillars of biological theory.

Evolution by Natural Selection

- A fundamental concept in evolutionary theory is “fitness”, which can be defined as the ability to survive and reproduce. Reproduction is key: to be evolutionarily fit, an organism must pass its genes on to future generations.
- Basic idea behind evolution by natural selection: the more fit individuals contribute more to future generations than less fit individuals. Thus, the genes found in more fit individuals ultimately take over the population.
- Natural selection requires 3 basic conditions:
 - 1. there must be inherited traits.
 - 2. there must be variation in these traits among members of the species.
 - 3. some inherited traits must affect fitness

Fitness

- Darwin didn't understand how inheritance worked--Mendel's work was still in the future. It wasn't until the 1930's when Mendelian genetics was incorporated into evolutionary theory, in what is called the "Neo-Darwinian synthesis".
- Translated into Mendelian terms, the basis for natural selection is that alleles that increase fitness will increase in frequency in a population.
- Thus, the main object of study in evolutionary genetics is the frequency of alleles within a population.
- A "population" is a group of organisms of the same species that reproduce with each other. There is only one human population: we all interbreed.
- The "gene pool" is the collection of all the alleles present within a population.
- We are mostly going to look at frequencies of a single gene, but population geneticists generally examine many different genes simultaneously.

Genetics of Populations

- Each diploid individual in the population has 2 copies of each gene. The allele frequency is the proportion of all the genes in the population that are a particular allele.
- The genotype frequency of the proportion of a population that is a particular genotype.
- For example: consider the MN blood group. In a certain population there are 60 MM individuals, 120 MN individuals, and 20 NN individuals, a total of 200 people.
- The genotype frequency of MM is $60/200 = 0.3$.
- The genotype frequency of MN is $120/200 = 0.6$
- The genotype frequency of NN is $20/200 = 0.1$
- The allele frequencies can be determined by adding the frequency of the homozygote to 1/2 the frequency of the heterozygote.
- The allele frequency of M is 0.3 (freq of MM) + $1/2 * 0.6$ (freq of MN) = 0.6
- The allele frequency of N is $0.1 + 1/2 * 0.6 = 0.4$
- Note that since there are only 2 alleles here, the frequency of N is $1 - \text{freq}(M)$.

Allele and Genotype Frequencies

- A gene is called “polymorphic” if there is more than 1 allele present in at least 1% of the population. Genes with only 1 allele in the population are called “monomorphic”. Some genes have 2 alleles: they are “dimorphic”.
- In a study of white people from New England, 122 human genes that produced enzymes were examined. Of these, 51 were monomorphic and 71 were polymorphic. On the DNA level, a higher percentage of genes are polymorphic.
- Heterozygosity is the percentage of heterozygotes in a population. Averaged over the 71 polymorphic genes mentioned above, the heterozygosity of this population of humans was 0.067.

Heterozygosity and Polymorphism

- Early in the 20th century G.H. Hardy and Wilhelm Weinberg independently pointed out that under ideal conditions you could easily predict genotype frequencies from allele frequencies, at least for a diploid sexually reproducing species such as humans.
- For a dimorphic gene (two alleles, which we will call A and a), the Hardy-Weinberg equation is based on the binomial distribution:
$$p^2 + 2pq + q^2 = 1$$
where p = frequency of A and q = frequency of a, with $p + q = 1$.
- p^2 is the frequency of AA homozygotes
- $2pq$ is the frequency of Aa heterozygotes
- q^2 is the frequency of aa homozygotes
- H-W can be viewed as an extension of the Punnett square, using frequencies other than 0.5 for the gamete (allele) frequencies.

Hardy-Weinberg Equilibrium

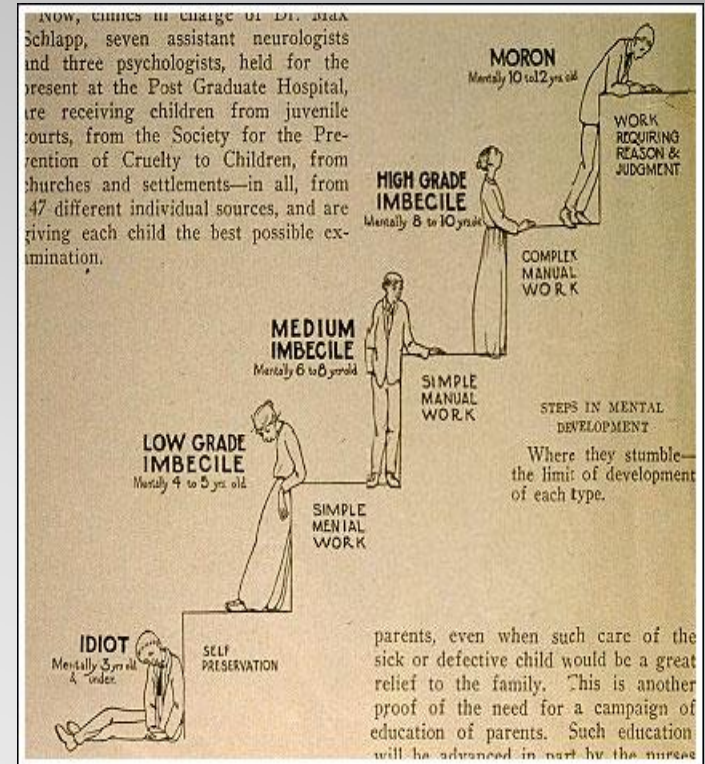
- Taking our previous example population, where the frequency of M was 0.6 and the frequency of N was 0.4.
- $p^2 = \text{freq of MM} = (0.6)^2 = 0.36$
- $2pq = \text{freq of MN} = 2 * 0.6 * 0.4 = 0.48$
- $q^2 = \text{freq of NN} = (0.4)^2 = 0.16$

- These H-W expected frequencies don't match the observed frequencies. We will examine the reasons for this soon.

Hardy-Weinberg Example

Rare Alleles and Eugenics

- A popular idea early in the 20th century was “eugenics”, improving the human population through selective breeding. The idea has been widely discredited, largely due to the evils of “forced eugenics” practiced in certain countries before and during World War 2. We no longer force “genetically defective” people to be sterilized.
- However, note that positive eugenics: encouraging people to breed with superior partners, is still practiced in places.
- The problem with sterilizing “defectives” is that most genes that produce a notable genetic disease are recessive: only expressed in homozygotes. If you only sterilize the homozygotes, you are missing the vast majority of people who carry the allele.
- For example, assume that the frequency of a gene for a recessive genetic disease is 0.001, a very typical figure. Thus $p = 0.999$ and $q = 0.001$. Thus $p^2 = 0.998$, $2pq = 0.002$, and $q^2 = 0.000001$. The ratio of heterozygotes (undetected carriers) to homozygotes (people with the disease) is 2000 to 1: you are sterilizing only 1/2000 of the people who carry the defective allele. This is simply not a workable strategy for improving the gene pool.



Die Deutung des Untermenschen.

Es treffen auf:

Männliche
Verbrecher



4,9 Kinder

Eine kriminelle
Ehe



4,4 Kinder

Eltern von
Hilfsschulkindern



3,5 Kinder

Die deutsche Familie



2,2 Kinder

Ehe aus gebildeten Kreisen



1,9 Kinder

"The Threat of the Underman. It looks like this: Male criminals had an average of 4.9 children, criminal marriage, 4.4 children, parents of slow learners, 3.5 children, a German family 2.2 children, and a marriage from the educated circles, 1.9 children."

- If Hardy-Weinberg equilibrium is assumed (an assumption we will examine shortly), it is possible to estimate the allele frequencies for a gene that shows complete dominance even though heterozygotes can't be distinguished from the dominant homozygotes.
- The frequency of recessive homozygotes is q^2 . Thus, the frequency of the recessive allele is the square root of this. Very simple.
- For example, the recessive genetic disease PKU has a frequency in the population of about 1 in 10,000. q^2 thus equals 0.0001 (10^{-4}). The square root of this is 0.01 (10^{-2}), which implies that the frequency of the PKU allele is 0.01 and the frequency of the normal allele is 0.99. Thus the frequency of the heterozygous genotype is $2 * 0.99 * 0.01 = 0.198$. About 2% of the population is a carrier of the PKU allele.
- Note again: this ASSUMES H-W equilibrium, and this assumption is not always true.

Estimating Allele Frequencies from Recessive Homozygote Frequency

- The relationship between allele frequencies and genotype frequencies expressed by the H-W equation only holds if these 5 conditions are met. None of them is completely realistic, but all are met approximately in many populations.
- If a population is not in equilibrium, it takes only 1 generation of meeting these conditions to bring it into equilibrium. Once in equilibrium, a population will stay there as long as these conditions continue to be met.
 - 1. no new mutations
 - 2. no migration in or out of the population
 - 3. no selection (all genotypes have equal fitness)
 - 4. random mating
 - 5. very large population

Necessary Conditions for Hardy-Weinberg Equilibrium

- If we have a population where we can distinguish all three genotypes, we can use the chi-square test once again to see if the population is in H-W equilibrium. The basic steps:
 - 1. Count the numbers of each genotype to get the observed genotype numbers, then calculate the observed genotype frequencies.
 - 2. Calculate the allele frequencies from the observed genotype frequencies.
 - 3. Calculate the expected genotype frequencies based on the H-W equation, then multiply by the total number of offspring to get expected genotype numbers.
 - 4. Calculate the chi-square value using the observed and expected genotype numbers.
 - 5. Use 1 degree of freedom (because there are only 2 alleles).

Testing for H-W Equilibrium

- Data: 26 MM, 68 MN, 106 NN, with a total population of 200 individuals.
- 1. Observed genotype frequencies:
 - MM: $26/200 = 0.13$
 - MN: $68/200 = 0.34$
 - NN: $106/200 = 0.53$
- 2. Allele frequencies:
 - M: $0.13 + 1/2 * 0.34 = 0.30$
 - N: $0.53 + 1/2 * 0.34 = 0.70$
- 3. Expected genotype frequencies and numbers:
 - MM: $p^2 = (0.30)^2 = 0.09$ (freq) $\times 200 = 18$
 - MN: $2pq = 2 * 0.3 * 0.7 = 0.42$ (freq) $\times 200 = 84$
 - NN: $q^2 = (0.70)^2 = 0.49$ (freq) $\times 200 = 98$
- 4. Chi-square value:
 - $(26 - 18)^2 / 18 + (68 - 84)^2 / 84 + (106 - 98)^2 / 98$
 - $= 3.56 + 3.05 + 0.65$
 - $= 7.26$
- 5. Conclusion: The critical chi-square value for 1 degree of freedom is 3.841. Since 7.26 is greater than this, we reject the null hypothesis that the population is in Hardy-Weinberg equilibrium.

Example

- The fullest meaning of “random mating” implies that any gamete has an equal probability of fertilizing any other gamete, including itself. In a sexual population, this is impossible because male gametes can only fertilize female gametes.
- More or less random mating in a sexual population is achieved in some species of sea urchin, which gather in one place and squirt all of their gametes, male and female, out into the open sea. The gametes then find each other and fuse together to become zygotes.
- In animal species, mate selection is far more common than random fertilization. A very general rule is “assortative mating”, that like tends to mate with like: tall people with tall people, short people with short people, etc. This rule is true for externally detectable phenotypes such as appearance, but invisible traits like blood groups are usually close to H-W equilibrium in the population.
- Assortative mating is most easily analyzed as a tendency for inbreeding. You are more like your relatives than you are to random strangers. Thus you are somewhat more likely to mate with a distant relative than would be expected by chance alone.

Relaxing the H-W Conditions: Random Mating

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Editor Signature

Momiao Xiong

Thank you.