Basics in Population Genetics

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- An application of population genetics
  - What are the genotypes causing G6PD deficiency that show resistance to malaria?
    - Which G6PD allele shows increased heterozygosity (decreased homozygosity) in mild malaria and increased homozygosity in severely diseased patients?
- Introduction to population genetics
  - Hardy-Weinberg Equilibrium (HWE)
    - Allele and genotype frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences.
  - Hardy-Weinberg Equation
    - The relationship between observed genotype frequency and the allele frequency in this equilibrium.
  - Deviation from HWE and possible causes

1. Human Population Genetics: an application

- Article: Sirugo G, Predazzi IM, Bartlett J, Tacconelli A, Walther M, Williams SM. **G6PD A- deficiency and severe malaria in The Gambia: heterozygote advantage and possible homozygote disadvantage.** *Am J Trop Med Hyg*. 2014 May;90(5):856-9.
- doi:10.4269/ajtmh.13-0622. Epub 2014 Mar 10. PubMed PMID: 24615128; PubMed Central PMCID: PMC4015578.

Abstract:
Glucose-6-phosphate dehydrogenase (G6PD) deficiency is frequent in Africa, because it confers resistance to *Plasmodium falciparum* malaria; however, the nature of the protection and the genotypes associated with it have been controversial. In 1972, Bienzle and others described **protection from malaria in West African females heterozygous for G6PD A-**. They determined that G6PD A- heterozygotes had lower parasite counts than A- homozygotes, hemizygous males, and normal individuals. However, other studies have reached different conclusions about the protective genotypes. DNA samples from 135 children with severe malaria and 146 children with mild malaria from The Gambia were genotyped for the G6PD A- mutation that is most frequent among Gambians (G6PD 968 T->C); there was a marked **deficiency of heterozygotes** and an **excess of homozygotes with severe malaria**, producing a **strong deviation from Hardy-Weinberg equilibrium**. Our results support the **protective effect in G6PD A- heterozygous females** and suggest that homozygotes might be more susceptible to severe malaria attacks.

Check List

- Describe the genomic location of the human G6PD gene and its role. Summarize relevant description in an OMIM entry
  - http://www.omim.org/entry/305900
- What are the clinical features of G6PD deficiency? Summarize relevant description in an OMIM entry
  - http://www.omim.org/entry/300908
- Describe the definition of the case-control study.
- Describe the target population of this study.
  - Especially, enrollment criteria, ages, and the sex composition.
- Describe the definition for “mild” and “severe” malaria in this study.
  - Also, describe the characteristic symptoms of “severe” population in this study.
- Describe the tested variants in this study. Which one is mainly discussed in this article?
- Describe deviation from HWE in females with severe malaria. See Table 3.
- Which genotype seems most advantageous against malaria? See Table 5.
  - Also, describe the results of statistical tests to support or not support the impression. See Table 6, 7, and 8.

2. Introduction to population genetics

- References on introduction to population genetics
  - 1. “Population Genetics” in http://cyberbridge.mcb.harvard.edu/
    - Evolution at the Population Level
    - What Does Genetics Have to Do With Population?
    - Hardy-Weinberg Principle
    - What Will Happen in the Next Generation?
    - Natural Selection
  - 2. “Evolution 101” in http://evolution.berkeley.edu/evolibrary/article/evo_01

Hardy-Weinberg law

- **If** an infinitely large, random mating population is free from outside evolutionary forces (i.e. mutation, migration and natural selection),
- **then** the gene frequencies will not change over time and the frequencies in the next generation will be p^2 for the ***AA*** genotype, $2pq$ for the ***Aa*** genotype and q^2 for the ***aa*** genotype.

https://www.ndsu.edu/pubweb/~mcclean/plsc431/popgen/popgen3.htm

Calculation of allele frequency

- See “The Hardy-Weinberg Law” in *Population and Evolutionary Genetics*
  - https://www.ndsu.edu/pubweb/~mcclean/plsc431/popgen/popgen3.htm

Assumptions for HWE

- Infinitely large population
- Random mating
- No evolutionary forces affecting the population
  - Selection
  - Migration (gene flow)
  - Mutation
  - Genetic drift

https://www.ndsu.edu/pubweb/~mcclean/plsc431/popgen/popgen3.htm

http://evolution.berkeley.edu/evolibrary/article/evo_14

Using deviation from HWE

- References on “heterozygote advantage”
  - Wikipedia “Heterozygote advantage”
    - https://en.wikipedia.org/wiki/Heterozygote_advantage
- References on “loss of heterozygosity”
  - Wikipedia “Loss of Heterozygosity”