Inheritance of Cancer

Steven A. Frank

A single inherited mutant gene may be enough to cause a very high cancer risk. Single-mutation cases have provided much insight into the genetic basis of carcinogenesis, but they are relatively rare and account for only a small fraction of all cancers. Examples include mutation to the *APC* gene, causing early onset colon cancer in the syndrome familial adenomatous polyposis (tumorous polyp-tissue in the colon); mutation to either the *BRCA1* or *BRCA2* genes, causing an increased risk of breast cancer; and mutation to the *TP53* gene, causing Li-Fraumeni syndrome with various early onset cancers such as bone or soft tissue sarcoma (Vogelstein and Kinzler, 2002).

Cancers sometimes cluster in families, but do not follow the rigid inheritance pattern characteristic of a mutation to a single gene. Males with a brother or father who has suffered prostate cancer are more likely to develop the disease. Similarly, females with a sister or mother who has suffered breast cancer are more likely to get a breast tumor. Some of the clustering may arise from the common diet and environment shared by families. Recently, however, researchers have begun to assign a significant fraction of cancer risk to the particular genetic variants that individuals inherit (de la Chapelle, 2004; Frank, 2004).

It may be that each genetic variant carried by an individual typically contributes only a small amount to cancer risk. Individuals who inherit several cancer-prone genetic variants may account for a significant fraction of all cancers. The degree to which such genetic tendencies portend cancer risk depends on how many different genetic variants exist in the population and whether those variants are common or rare.

New genetic technologies provide the tools to measure genetic variation in populations. Interpreting these data in terms of cancer risk presents challenges, because it is often difficult to match the observed variations in DNA sequence to their consequences for cancer risk. The subject of population genetics provides some guidelines about how to interpret the current data and what we might expect to learn in the future about the inheritance of cancer risk (Frank, 2004). At the same time, advances in the molecular biology of cancer provide strong clues about the kinds of genes that are likely to influence inherited cancer risk, such as genes that control DNA repair, regulation of the cell cycle, and the signals that influence cellular proliferation and death (Vogelstein and Kinzler, 2002).

Single Genes With a Large Effect on Cancer Risk

To understand the inheritance of cancer risk, we need to understand what causes particular mutations to rise or fall in frequency in populations. It is useful to start with the single-gene mutations that have large effects on cancer risk. Although such mutations account for only a small fraction of all cancer risk, their simplicity allows us to match identifiable cancer syndromes to particular genes, providing a test case for understanding what determines the frequency of variant genes in populations.

There are few direct estimates for the frequencies of mutations that cause a high risk of cancer. Direct estimates actually count the number of mutated and unmutated alleles in the population by screening for molecular differences in genes. Some rough estimates have

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been given for the frequency of cases, from which we can make some crude calculations about the frequency of mutated genes. For example, inherited cases of retinoblastoma, Wilms tumor (kidney tumor in young children), and skin cancer in xeroderma pigmentosum (a disorder in which there is a hypersensitivity to light ultimately resulting in skin cancer) all occur roughly at frequencies of 1 per 10,000 or 100,000 individuals (Vogelstein and Kinzler, 2002). Most individuals carrying a severe mutation express a serious or fatal disease in childhood or early life, so the frequency of cases is about the same as the frequency of the mutated gene in the population.

Suppose a mutant gene leads to cancer in all individuals who carry the mutation, and the carriers die before they have reproduced. In this situation, each case must arise from a new mutation, and the frequency of mutated genes is roughly the probability of a new mutation arising. To explain an early onset cancer syndrome that occurs in 1 per 10,000-100,000 individuals, the rate at which new mutations arose would be about the same magnitude. The rate of new mutations to a gene in each generation is usually estimated to be a bit lower, about 1 per 100,000-1,000,000 births. Thus, for these severe early onset cancers, the frequency of the mutant gene in the population is close to, but perhaps just a bit higher than, the frequency at which new mutations arise.

Other factors might influence the frequency of mutant genes in the population. Some genes could have higher mutation rates than others, and some individuals who carry a mutation might reproduce and transmit the mutation to their progeny. Overall, the observed rates of cancers such as retinoblastoma, Wilms tumor, and skin cancer in xeroderma pigmentosum seem to be readily explained by a simple balance between the gain by new mutations and the loss by early death.

Later Onset

Mutations in the *APC* gene cause the colon cancer syndrome familial adenomatous polyposis. Nearly all carriers develop cancer, with a median age of onset of about 40. The frequency of cases is about 1 per 10,000 individuals.

If an individual carries an *APC* mutation, but manages to reproduce before disease causes mortality or severe morbidity, then in that case, the disease does not reduce the frequency of the mutation in the population. Suppose, for example, that in the past, a carrier of an *APC* mutation had an average loss of reproduction of 10% from early morbidity or mortality. From the point of view of transmitting the mutation, this is the same as 1 in 10 individuals failing to reproduce, and the other 9 individuals reproducing normally. So the frequency of cases would be 1 per 10,000, but the frequency of lost reproduction would be 1 per 100,000, about the same frequency at which new mutations arise. Again, we see an approximate balance between new mutations and loss of mutations from death before reproduction.

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In general, the frequency of new mutations roughly balances the loss in reproduction per case multiplied by the frequency of cases. So, the later the age of cancer onset and the lower the loss in reproduction, the higher the frequency of cases.

Lower Risk

In the previous examples, an individual carrying a mutation almost always develops cancer. Other mutations may increase cancer risk relative to normal individuals, but the risk to a carrier of developing cancer may still be less than 100%.

Mutations to *BRCA1* cause carriers to have about a 55-85% chance of developing breast cancer, with a median age of onset of about 50 years (Vogelstein and Kinzler, 2002). The combination of partial expression and typi-

cal onset after the age of reproduction means that many carriers pass on their mutation. Consequently, the frequency of *BRCA1* mutations in populations is roughly 1 per 100 to 1 per 1,000, higher than for the mutations that always cause early onset cancer.

Particular mutations to *HRAS1*, *BLM*, and other genes have been associated with an approximately two-fold increase in colorectal cancer risk (de la Chapelle, 2004). Although these mutations may cause an increased risk, most carriers do not develop colorectal cancer, and those who do tend to develop the disease later in life. The loss in reproduction for carriers of these mutations is small, and the associated frequencies of carriers tends to be high, in the range of 1 per 100 to 1 per 10 individuals in certain populations. In general, the lower the frequency at which a particular mutation leads to cancer, the smaller the loss in reproduction and the higher the frequency of individuals who carry the mutation.

Multiple Genes

Humans have five major systems to repair DNA damage (Bernstein et al., 2002). Inherited mutations to the DNA repair systems increase the accumulation of somatic mutations in cells that arise during cellular division. The accumulation of somatic mutations in cells over a lifetime is thought to be a major factor in cancer progression (Vogelstein and Kinzler, 2002).

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Individuals who inherit mutations to the DNA mismatch repair system tend to accumulate more somatic mutations in their cells during growth and tissue renewal. Individuals with an inherited reduction in mismatch repair capacity frequently suffer hereditary nonpolyposis colon cancer or Lynch syndrome (de la Chapelle, 2004). The frequency of cases is at least 1 per 1,000 individuals, but may be more frequent because hereditary nonpolyposis cases can be difficult to distinguish from colon cancers that arise without mismatch repair defects.

There are 22 genes in the core DNA mismatch repair pathway. Although so far, mutations that increase hereditary nonpolyposis colon cancer have been identified in five mismatch repair gene loci, mutations that influence this disease probably occur in other mismatch repair genes as well. The point here is that as the number of genes in a pathway increases, there is a greater chance for new mutations to disrupt the pathway and lead to disease. As the number of genes that affect a particular cancer rises, the frequency of inherited mutations that predispose to that cancer increases.

Multiple Genes Each With a Small Effect on Cancer Risk

So far, I have presented a series of examples in which the deleterious effect of each particular mutated gene has become weaker and the frequency of individuals carrying mutations to those genes has risen. In addition, the previous example shows that we must also account for multiple genes that can cause a particular cancer.

Ideally, I would be able to continue this trend, discussing a series of mutations that cause weaker risk per mutation and have higher population frequencies of mutations per gene, and for which there are more genes that affect cancer risk. I would then be discussing the way in which many different genes, each with mutational variants of small effect, combine to determine the inherited risk of cancer.

Polymorphism of DNA Repair Genes

In particular, one would like to know how genetic variants affect the biochemistry of cells, and how those biochemical effects influence the progression to cancer. Although we are still a long way from this ideal, recent studies of DNA repair genes provide hints about what could be learned.

Individuals vary in their ability to repair DNA damage. Relatively low repair efficiency is associated with a

higher risk of cancer. Presumably, the association arises because a higher rate of unrepaired somatic mutations and chromosomal aberrations contribute to a faster progression to cancer.

Most studies of repair capacity measure the effect of mutagens on DNA damage to lymphocytes. For example, a mutagen can be applied to cell cultures of lymphocytes. After a period of time, damage can be measured by unrepaired single-strand or double-strand DNA breaks, or by incorporation of a radioisotope.

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Roughly speaking, DNA repair efficiency has an inheritance pattern that is typical of many characters. A few rare mutations cause large deficiencies in repair capacity. Apart from these rare cases, repair capacity varies continuously and has a significant inherited component. Measures of variability and heritability are statistical descriptions of the genetics of DNA repair. Recent studies have just made the first steps toward understanding the mechanistic relations between genetic variants and altered phenotype (traits).

Many genes in the five key repair pathways for different types of DNA damage are known, so genetic variants can be identified by sequencing the DNA. Particular variants can also be constructed, and their physiological consequences tested in cell assay systems. Mohrenweiser et al. (2003) list 22 genes in the core pathway of the mismatch repair system, which I discussed above in the context of hereditary nonpolyposis colon cancer. This system primarily corrects DNA mismatches and short insertion or deletion loops that arise during DNA replication or recombination. The mismatch repair system improves DNA replication accuracy by a factor of 100-1000.

In 17 different DNA mismatch repair genes screened in at least 50 unrelated individuals, 85 different variants have been found. Of these variants, 38% occurred at a frequency of 2% or more; 21% occurred at a frequency of 5% or higher; and 12% occurred at a frequency of 20% or higher. Similar results were obtained for the other DNA repair pathways summarized by Mohrenweiser et al. (2003). In 74 repair genes from various pathways, the average frequency of the common allele is approximately 80%, with the remaining 20% comprised of various allelic variants. Among the 148 alleles per person at the 74 repair loci, the average number of allelic variants is expected to be roughly 30. Presumably each individual will carry a very rare or unique genotype.

"So, small variations in DNA repair are highly heritable, DNA repair efficiency is correlated with cancer risk, and there are widespread polymorphisms in the DNA sequence of the known repair genes. The next step is to link the polymorphisms to variations in the biochemistry of repair, providing a mechanistic understanding of how genetic variation influences an important aspect of cancer predisposition. In general, this provides a model for how in the future we will be able to relate inherited variations in DNA sequence to altered biochemistry, progression of disease, and patterns of inheritance."

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References and Further Readings

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