"Jewishness is not a matter of DNA. Our genes needn't be our destiny, nor should they be."

David B. Goldstein
Human Biology

Genomics

Today’s Lecture
Genes

A Gene...

• *Is made of DNA, the basic genetic material*
  
  – Carries the chemical instructions to make all the proteins in the body

• Each gene has the “code” for one particular protein

• *We have two copies of most genes*
A **Eukaryote** is any organism whose cells contain a nucleus and other organelles enclosed within membranes.
Eukaryotic Cell

- Mitochondria
- Nucleus
- Chromatin
- Ribosomes
Karyotype vs Genotype vs Phenotype

- **Karyotype**
  - Chromosomal pattern

- **Genotype**
  - Entire genetic constitution

- **Phenotype**
  - Physical and physiological makeup
  - e.g., short stature, infertility, osteoporosis
Karyotypes describe the number of chromosomes (46), and what they look like under a light microscope.

- In diploid organisms (humans) autosomal chromosomes (44) are present in two copies.
- There is also a pair of sex chromosomes (X & Y).
Sex Chromosomes

X

Y
Dr. Karl Skorecki
Dr. Karl Skorecki

• The only child of Holocaust survivors, *Karl Skorecki was born and educated in Toronto*, where he received his MD degree from the University of Toronto in 1977.

• Between 1977-1984, he pursued postgraduate clinical and research training in internal medicine, nephrology, and molecular biology at Harvard Medical School in Boston.

• In 1995, *Skorecki* joined the staff of *Rambam Health Care Campus (Rambam)* and the *Technion-Israel Institute of Technology’s (the Technion)* Ruth and Bruce Rappaport Faculty of Medicine in Haifa.
Dr. Karl Skorecki

- **Prof. Skorecki** is currently **Director of Medical and Research Development at the Technion**.
- He conducts research in human molecular genetics and stem cell biology.
- **Skorecki’s interest in population genetics began with a series of research studies tracing patrilineal genealogies in the Jewish priesthood and shared ancestries of Diaspora Jewish communities.**
Max & The Rabbi
Cohanim

- **Cohanim** (plural of Cohen) are the priestly family of the Jewish people, members of the Tribe of Levi.
- The books of Exodus and Leviticus describe the responsibilities of the Cohanim, which include the Temple service and blessing of the people.
Cohanim

• Jewish tradition, based on the Torah, is that all Cohanim are direct descendants of Aaron, the brother of Moses.

• The Cohen line is patrilineal
  – Passed from father to son without interruption for 3,300 years, or more than 100 generations.
• The *Y chromosome* consists almost entirely of *Non-coding DNA* (except for the genes determining maleness).

• Since it is passed from father to son without recombination, the *genetic information on a Y chromosome of a man living today is basically the same as that of his ancient male ancestors*.

• A combination of these *neutral mutations*, known as a *Haplotype*, can serve as a genetic signature of a man’s male ancestry.
The Cohen Genes

• In the first study by Dr. Skorecki, et al (Nature; January 2, 1997), 188 Jewish males were asked to contribute some cheek cells from which their DNA was extracted for study.

• Participants from Israel, England and North America were asked to identify whether they were a Cohen, Levi or Israelite, and to identify their family background.
The Cohen Genes

• The results of the analysis of the Y chromosome markers of the Cohanim and non-Cohanim were indeed significant.

• A particular marker, (YAP) was detected in 98.5% of the Cohanim, and in a significantly lower percentage of non-Cohanim.
The Cohen Genes

• In a second study, Dr. Skorecki and associates gathered more DNA samples and expanded their selection of Y chromosome markers.

• They found that a particular array of six chromosomal markers was found in 97 of the 106 Cohens tested.
The Cohen Modal Haplotype

- *This collection of markers has come to be known as the Cohen Modal Haplotype (CMH)—the standard genetic signature of the Jewish priestly family.*

- The chances of these findings *happening at random* is greater than one in 10,000.
The Cohen Modal Haplotype

- The finding of a common set of genetic markers in both Ashkenazi and Sephardi Cohanim worldwide clearly indicates an origin pre-dating the separate development of the two communities around 1000 CE.

- Date calculation based on the variation of the mutations among Cohanim today yields a time frame of 106 generations from the ancestral founder of the line, some 3,300 years—the approximate time of the Exodus from Egypt, the lifetime of Aaron HaCohen.
The Torah & The Cohanim

• The research findings support the Torah statements that the line of Aaron will last throughout history:
  
  – “… and they shall have the Priesthood as a statute forever, and you shall consecrate Aaron and his sons.” [Exodus 29:9]
  
  – “… it shall be for them an appointment to an everlasting Priesthood throughout their generations.” [Exodus 40:15]
  
  – “And it shall be to him and to his descendants after him a covenant of everlasting Priesthood.” [Numbers 25:13]
The Cohanim

• For over 2,000 years and despite their having been scattered throughout the world, **the extended family of Cohanim have maintained their genetic integrity** equivalent to the highest percentages of the other Middle Eastern groups which never left the region.
The Cohanim

• **Jewish is not a genetic definition**
  
  – Other peoples, through marriage and conversions, have joined the Jewish People.

• However, **being a Cohen is a genetic definition—father to son starting from Aaron, the High Priest.**
The Cohen Modal Haplotype

• The researchers’ policy is that *the research is not a test of individuals*, but an examination of the extended family.

• *Having the CMH is not a proof of one’s being a Cohen.*

• At present, there are no ramifications in Jewish law due to this discovery.

• *No one is certified nor disqualified because of their Y chromosome markers.*
“My Yiddishe Momma”
“My Yiddishe Momma”

• For most of the history of the Diasporan Jewish experience it has been the mother who has determined religious identity.

  – If your mom was Jewish, you were Jewish.

• The Babylonian Talmud was clear:

  – “Thy son by an Israelite woman is called thy son, and thy son by a heathen is not called thy son but her son” (Kiddushin 68b).
“My Yiddishe Momma”

• From that point on (circa 550-700 C.E.), the custom was followed by all major branches of Judaism until the late twentieth century.

• Then some Jewish movements in North America relaxed or abolished the use of matrilineal descent as a criterion for Jewishness.
The “X” Factor

• Unlike most of the Y, the female X undergoes the genetic reshuffling process that drives evolution with every conception.

• Thus, whereas the Y is transmitted nearly unchanged over many generations, the X is much more dynamic and therefore more difficult to track backwards through time.
Mitochondria & Mitochondrial DNA
Mitochondria

• The **Mitochondria** are discrete packages, or **organelles**, found outside the nucleus of cells.

• These organelles are essential to cells because they are the site of the final breakdown of food and the subsequent liberation of energy (ATP).

• **In essence they are the power plants of the cell, and hence, the human body**
Sperm Mitochondria
**Pattern of inheritance:** Unlike nuclear DNA, which we inherit half from our mother and half from our father, mitochondrial DNA is passed on only by females. The reason is that when the sperm fertilizes the egg, it leaves behind all its mitochondria: the developing fetus therefore inherits mitochondria only from the mother’s egg.
Shuttle Loses SRB’s
Mitochondrial DNA

- There are about 1,700 in every human cell.
- Each *mitochondrion* includes an identical loop of DNA about 16,000 base pairs long containing 37 genes.
- In contrast, *nuclear DNA* consists of three billion base pairs and an estimated 70,000 genes.
Mitochondrial DNA

• Just as the Y chromosome is transmitted exclusively through the male line, mitochondrial DNA is inherited strictly through the female line.

• Although it is passed from mothers to both sons and daughters, sons do not pass on their mitochondrial DNA.

• The Y chromosome records the history of males in a population, and the mitochondrial DNA records the history of females.
Mitochondrial DNA

• **The mitochondrial genome is passed from mother to daughter intact.**

• Different mitochondrial DNA molecules do not usually mix with one another.

• This means that all the mitochondrial DNA on the planet, just like all the Y chromosomes on the planet, *share a single evolutionary history.*
Mitochondrial DNA

• The fact that mitochondrial DNA is maternally inherited enables genealogical researchers to trace maternal lineage far back in time.

• A 2006 study based on high-resolution analysis of Haplogroup K(mtDNA), suggested that about 40% of the current Ashkenazi population is descended matrilineally from just four women.
Mitochondrial DNA

- These were "founder lineages" that were "likely from a Hebrew/Levantine mtDNA pool" originating in the Middle East in the 1st and 2nd centuries CE.

- Moreover, a maternal line "sister" was found among the Jews of Portugal, North Africa, France, and Italy.
Mitochondrial DNA

- A 2013 study concluded that 65%-81% of Ashkenazi Mt-DNA is European in origin, including all four founding mothers, and that most of the remaining lineages are also European.

- The team analyzed about 2,500 complete and 28,000 partial Mt-DNA genomes of mostly non-Jews, and 836 partial Mt-DNA genomes of Ashkenazi Jews.

- *The study claims that only 8% of Ashkenazi Mt-DNA is Middle Eastern in origin*, and the origin of the rest is unclear.
Regarding the origin of Ashkenazi admixture, the analyses suggest that "the first major wave of assimilation probably took place in Mediterranean Europe, most likely in the Italian peninsula."

– There was substantial further assimilation of minor founders in west/central Europe.

The studies found less evidence for assimilation in Eastern Europe, and almost none for a source in the North Caucasus/Chuvashia.
Why So Many Jewish Genetic Diseases?

• *The Founder Effect*
  – The loss of genetic variation that occurs when a new population is established by a very small number of individuals from a larger population.
  – It explains how genes in small, isolated populations can spread and even come to dominate a gene pool.
  – Geneticists also call this the “Bottleneck Effect”
  • A shrinking of a population followed by a rapid expansion.
Changes in a population's allele frequency following a population bottleneck: the rapid and radical decline in population size has reduced the population's genetic variation.
Genetic Drift

- **Genetic Drift** is the establishment of certain alleles due to random sampling of the gene pool in small populations.
- Genetic drift refers to the net decrease in genetic variability and heterozygosity over time.
- In stable populations, genetic drift causes genetic variation to decrease significantly more quickly than mutation can add new variation.
- **Genetic Drift is a random genetic process.**
Genetic Drift

Random sampling and genetic drift

original population  second generation  third generation  fourth generation  fifth generation
• **Genetic Drift** and the **Bottleneck or Founder Effect** can **play dramatic roles in shaping geographically or culturally isolated populations, such as Jews.**

• If the community is small enough, even **harmful mutations** that drift into the population and that might otherwise be eliminated through natural selection **are preserved and can be quickly spread.**
Ashkenazi Jewish genetic disorders represent a varied group of conditions.

In general, 1 in 15 Ashkenazi Jews is a carrier for at least one of these disorders.

Some disorders are more common than others—carrier frequencies range from 1:15 to 1:127.
Disorders can differ by:

- **Age of onset**
- **Degrees of severity**
- **Treatment options**

**Genetic testing is now available for almost all the disorders.**
What is a genetic mutation and how does it lead to disease?

- A change in the DNA of a particular gene can result in an alteration of the genetic instructions.
- Some genetic alterations are not harmful but are part of our genetic differences (for example, hair color and eye color).
- **An alteration in a gene can lead to disease by affecting the function of that gene.**
Single Nucleotide Mutation

Point Mutation

DNA structure showing a point mutation.

2/22/2015
Leslie Pearlstein, MD, FACS
Many of the Ashkenazi Jewish genetic disorders are inherited in a **Recessive Fashion**.

When both parents are carriers for the same disorder, they have a 25% chance in each pregnancy of having an affected child.
Dominant & Recessive Genes

- **The terms dominant and recessive describe the inheritance patterns of certain traits.**
  - They describe how likely it is for a certain phenotype to pass from parent offspring.

- A dominant allele produces a dominant phenotype in individuals who have one copy of the allele, which can come from just one parent.
Dominant & Recessive Genes

• For a recessive allele to produce a recessive phenotype, the individual must have two copies, one from each parent.

• They are generally considered “carriers” of the recessive allele
  – The recessive allele is there, but the recessive phenotype is not.
Dominant & Recessive Inheritance

Recessive inheritance

- Carrier Father: NN
- Carrier Mother: Nn
- Offspring:
  - NN: Normal
  - Nn: Carrier
  - nn: Affected

1:4 Phenotype

Dominant inheritance

- Affected Father: Dd
- Normal Mother: dd
- Offspring:
  - Dd: Affected
  - dd: Normal

2:4 Phenotype

2/22/2015
## Ashkenazi Jewish Genetic Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Incidence</th>
<th>Carrier Frequency</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sacs Disease</td>
<td>1/3,000</td>
<td>1/30</td>
<td>98 %</td>
</tr>
<tr>
<td>Canavan Disease</td>
<td>1/6,400ß</td>
<td>1/40</td>
<td>98 %</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1/2,500-1/3,000</td>
<td>1/29</td>
<td>97 %</td>
</tr>
<tr>
<td>Familial Dysautonomia</td>
<td>1/3,600</td>
<td>1/32</td>
<td>99 %</td>
</tr>
<tr>
<td>Fanconemia Anemia</td>
<td>1/32,000</td>
<td>1/89</td>
<td>99 %</td>
</tr>
<tr>
<td>Nieman-Pick Disease</td>
<td>1/32,000</td>
<td>1/90</td>
<td>95 %</td>
</tr>
<tr>
<td>Mucolipoidosis IV</td>
<td>1/62,500</td>
<td>1/127</td>
<td>95%</td>
</tr>
<tr>
<td>Bloom Syndrome</td>
<td>1/40,000</td>
<td>1/100</td>
<td>96 – 97 %</td>
</tr>
<tr>
<td>Gaucher Disease</td>
<td>1/900</td>
<td>1/15</td>
<td>95 %</td>
</tr>
</tbody>
</table>
Tay-Sachs Disease

- **Tay-Sachs Disease** is a rare recessive gene disorder passed from parents to child.
- Carriers of a single Tay–Sachs allele do not exhibit symptoms of the disease but appear to be protected to some extent against tuberculosis.
- This accounts for the persistence of the allele in certain populations in that it *confers a selective advantage*—in other words, *being a heterozygote is advantageous.*
Tay-Sachs Disease

- In the most common form, a baby about 6 months old will begin to show symptoms.

- A child who inherits the gene from both parents develops Tay-Sachs disease.
Tay-Sachs Disease

• Tay-Sachs disease occurs most frequently among people whose ancestors come from Eastern and Central European Jewish communities (Ashkenazi Jews).

  • French Canadian communities in Quebec
  • Old Order Amish community in Pennsylvania
  • Cajun community of Louisiana.
Tay-Sachs Disease

- Tay-Sachs disease results when an enzyme that helps break down fatty substances is absent.
- These fatty substances build up to toxic levels in the child's brain and affect the nerve cells.
- As the disease progresses, the child's body loses function, leading to blindness, deafness, paralysis and death.
Tay-Sachs Disease

- **There is no cure for Tay-Sachs disease.**
- Three main approaches have been used to prevent or reduce the incidence of Tay–Sachs:
  - **Prenatal diagnosis**
    - If both parents are identified as carriers, prenatal genetic testing can determine whether the fetus could inherit a defective gene copy from both.
Tay-Sachs Disease

• Preimplantation genetic diagnosis
  • By retrieving the mother's eggs for in vitro fertilization, it is possible to test the embryo for the disorder prior to implantation.
  • Healthy embryos are then selected and transferred into the mother's womb.
Tay-Sachs Disease

- **Mate selection**
  - In Orthodox Jewish circles, the organization Dor Yeshorim carries out an anonymous screening program so that couples with *Tay–Sachs* or another genetic disorder can avoid conception.

- **Gene therapy replacement therapy may eventually lead to a cure or treatment to slow the progression of *Tay-Sachs disease*.**
Incidence of Classical Tay-Sachs disease in the U.S. and Canada

Number of Cases

Year Ending


Jewish

Non-Jewish
BRCA1 & BRCA2 Mutations

Breast Cancer & Genetics
BRCA₁ & BRCA₂ Gene Mutations

• Approximately **2.0%-2.5% of Ashkenazi Jewish women carry one of three founding mutations in the BRCA₁ and BRCA₂ (both dominant) genes**

• **Each mutation is associated with a high lifetime risk of invasive breast cancer.**
BRCA1 & BRCA2 Gene Mutations

- **Mutations in either gene confer up to 70-80% lifetime risk of Breast Cancer in carrier females.**
- Over 85 distinct BRCA1 mutations have been identified.
BRCA₁ & BRCA₂ Gene Mutations

- **Mutations in BRCA₁ account for approximately 45% of familial breast cancer and 90% of inherited breast/ovarian cancer.**

- Approximately **12%** of breast cancers in the Ashkenazi Jewish population are attributable to mutations in the **BRCA₁** or **BRCA₂ gene**.

- **88% of breast cancers** are due to other gene non-familial mutations.
BRCA Gene Mutations & Breast Cancer

- **Breast Cancer By Age 50**: Up to 50%
- **Breast Cancer By Age 70**: Up to 87%
- **Second Breast Cancer By Age 70**: Up to 64%
- **Ovarian Cancer By Age 70**: Up to 44%

Risk of Cancer (%)
BRCA1 & BRCA2: Associated Cancers

### Lifetime BRCA1 and BRCA2 Cancer Risks for Women

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Women with BRCA1 mutation</th>
<th>Women with BRCA2 mutation</th>
<th>Average women in US without mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>60-80%</td>
<td>50-70%</td>
<td>13%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>20-45%</td>
<td>10-20%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2-3%</td>
<td>3-5%</td>
<td>1%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>—</td>
<td>3-5%</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

### Lifetime BRCA1 and BRCA2 Cancer Risks for Men

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Men with BRCA1 mutation</th>
<th>Men with BRCA2 mutation</th>
<th>Average man in US without mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1-5%</td>
<td>5-10%</td>
<td>.1%</td>
</tr>
<tr>
<td>Prostate</td>
<td>*</td>
<td>15-25%</td>
<td>16%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2-3%</td>
<td>3-5%</td>
<td>1%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>—</td>
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<td>1-2%</td>
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</table>

*Although there is no convincing evidence of overall increased risk of prostate cancer, men with BRCA1 mutations may develop prostate cancer at a younger age than men in the general population. BRCA2 mutations are associated with an increased risk of prostate cancer, which also can be earlier onset.*
BRCA1 & BRCA2 Testing

To Test or Not To Test?
**BRCA1 & BRCA2 Genetic Testing**

- **How would Genetic Testing change the management of women with breast cancer?**
  - Increased surveillance of unaffected breast.
  - Consider prophylactic mastectomy.
  - Increased surveillance for ovarian cancer.
  - Consider prophylactic oophorectomy.
  - Pre-symptomatic mutation testing in extended family.
  - Administration of risk-reducing medications.
BRCA₁ & BRCA₂ Genetic Testing

• **Disadvantages of Genetic Testing**
  • Guilt & concern over passing gene mutation to other family members.
  • Worry of developing additional cancers.
Sephardic/Oriental Jewry and Genetic Diseases

• For the many purposes of identifying genetic disorders, *Sephardic and Oriental Jews* can be defined as any Jews who are not of Ashkenazi origin.

• However, this is a varied group with ancestors from Persia (Iran), Yemen, North Africa (e.g., Morocco, Tunisia), Spain, Italy, the Balkans, Iraq, India, etc.

• *These distinct subgroups of Jews evolved in the Middle East, Mediterranean and Far East with some disorders unique to each subpopulation.*
Sephardic/Oriental Jewry and Genetic Diseases

- Hereditary Inclusion Body Myopathy (HIBM)
- Wolman Disease
- Usher Syndrome (Type 2)
- Pseudocholinesterase deficiency (anesthesia sensitivity)
- Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency
Sephardic/Oriental Jewry and Genetic Diseases

- Thalassemia
- Congenital Hypoaldosteronism (salt-losing disorder):
  - Familial Mediterranean Fever (FMF)
  - Glycogen Storage Disease (Type III)
  - Polyglandular deficiency (multiple hormone deficiency)
Jewish Identity & Genomics

- From a demographic and genetic perspective one can see the history of the Jews as an intricate combination of forces, both genetic and cultural, woven together and operating with different strengths at different times.
Jewish Identity & Genomics

• “It’s metaphysical and not physical”

• “Our identity is based on an oral tradition, law, culture, custom, and not on physical attributes, including DNA. But genetics can tell us a great deal about origins and common ancestry. It can help us piece together how we survived over the centuries as a people.”

Glossary

• **Allele.** A specific form of a gene.

• **Autosomal Recessive.** Any trait coded for by a single gene on a non-sex chromosome requiring two copies, one from each parent. Cystic fibrosis, for example, is caused by two faulty copies of the CFTR gene, one inherited from each parent.

• **Base Pair.** Two nucleotides (DNA or RNA subunits) on opposite complementary DNA or RNA strands that are connected via hydrogen bonds.

• **Chromosomes.** Rod-like bodies resident in the nucleus of cells containing the chemical chromatin and a subset of an organism's genome (some organisms have only one chromosome). Their numbers are relatively constant in the cells of any one kind of organism. Humans have twenty-three pairs of chromosomes.
Glossary

- **Cohen Modal Haplotype (CMH).** A set of genetic markers that are usually inherited together on the male Y chromosome and that have been statistically associated with priestly origins among self-identified Jews.

- **DNA.** Deoxyribonucleic acid, a nucleic acid found in cell nuclei and especially genes that is associated with the transmission of genetic information.

- **Endogamous Group.** A community in which members generally mate within the group.

- **Forensic DNA.** One or more DNA samples obtained from a crime scene or mass disaster.
Gene. A discrete stretch of DNA that can be transcribed into RNA that is usually (but not always) translated into protein.

Genealogy. A historical account of the descent or ancestry of a person, family, or group.

Genetics. The study of inheritance, often focused on just one gene or a few genes and/or traits.

Genome. The entire DNA content of an organism. For example, the human genome consists of roughly three billion base pairs of DNA. The roundworm genome is roughly 100 million base pairs.

Genomics. The study of genomes or parts of genomes, generally undertaken on a larger scale than traditional genetics.
Glossary

- **Haplogroup.** A large set of haplotypes.
- **Haplotype.** A group of alleles within one or more genes occurring on a single chromosome that are close enough to one another to usually be inherited as a unit.
- **Microsatellite.** A polymorphic DNA marker that usually consists of repeating units of one to four base pairs in length. Because microsatellites exist in so many forms and can therefore be traced through multiple generations and kinships, they are especially useful for population genetic studies.
- **Mutation.** A permanent physical change in the sequence of DNA or RNA.
- **Polymorphic Markers.** Genetic variants that exist in two or more forms. Polymorphic markers are essential for understanding how traits and diseases are inherited; they serve as signposts for those traits.
• **Polymorphism.** A genetic variant that exists in two or more forms. Polymorphisms are invaluable for genetic studies because of their association with particular traits.

• **Regulation of gene expression.** Control of the extent to which a gene is turned on or off. Gene expression is often regulated by DNA sequences that are not genes themselves.

• **RNA.** A close chemical relative of DNA but used in a different way. Whereas DNA is primarily responsible for transmitting information between the generations, RNA acts as a message system within the body carrying instructions from the DNA about how to build proteins. Recently it has also been shown that RNA can have a variety of important functions in its own right.
References

• Jewish Genetic Disease Consortium
  – http://www.jewishgeneticdiseases.org/jewish-genetic-diseases/

• Legacy: A Genetic History of the Jewish People by Harry Ostrer
  – Publisher: Oxford University Press; 1 edition (May 2, 2012)

• Jacob's Legacy: A Genetic View of Jewish History by David B. Goldstein
  – Publisher: Yale University Press; First Edition edition (May 28, 2008)

• Abraham's Children: Race, Identity, and the DNA of the Chosen People by Jon Entine
  – Publisher: Grand Central Publishing (October 24, 2007)
  – ASIN: B000WQ10VU