Genetics, biodiversity, agriculture

Environmental Health (5)
Frumkin's textbook 3rd ed. Chapter 7, 18 & 19

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Chapter 7. Genes, Genomics and Environmental Health

- Key concepts
  - DNA, as the "blueprint of life", is the principal biological template that allows all living organisms to reproduce and pass on their fundamental attributes to offspring.
  - Other factors than DNA, *epigenetics*, can modify how genes are expressed.
  - Environmental factors, including diet, chemical exposures, and lifestyle (e.g., smoking and alcohol consumption), may interact with both genetic and epigenetic processes.
  - Interindividual differences in susceptibility to environmental pollutants may be determined by both genetic and epigenetic processes.
  - Molecular tools (so-called *omics technologies*) that can quickly and cheaply acquire millions of biological data points have transformed how scientists study the causal relationships between environmental exposures and disease outcomes.
  - Big data obtained by omics can be analyzed by mathematics, statistics and computation.

Basic Components of Gene and Genome

- Living organism uses a string of chemicals, called bases + deoxyribose = DNA (deoxyribonucleic acid)
  - 4 bases: T (thymine), G (guanine), C (cytosine), A (adenine)
  - DNA is double strand (complementary each other)
  - Fixed pairs of A and T, G and C
  - If a strand of DNA has the nucleotide sequence CGTCCGAT, the other must be GCAGGCTA
  - Triplet theory: 3 bases (codon) code one amino acid → 2 or 3 different codons for the same amino acid
- Approx. 3 billions of base pairs constitutes human genome
- Each cell has the same set of DNA, but expression is different by cell or tissue
- Gene is a specific sequence of nucleotides that contains information and that controls some function in the cell
- Approx. 24,000 genes in human genome
- Genome (genes within it) is composed of discrete units (chromosomes)
  - Human has 46 chromosomes (22 pairs of autosomes + 2 sex-specific chromosomes), 23 from the mother in egg, 23 from the father in sperm
  - Females' sex-specific chromosomes are XX
  - Males' sex-specific chromosomes are XY. Y from father.
- Within a chromosome, genes are located in the specific positions (loci).

Human genome and elements of gene (cited from Frumkin's text Chap. 7)

Figure 7.1 & Figure 7.2

Types of genetic variability

- Differences in single nucleotides in the same position of the same locus are the most common type of genetic variability, single nucleotide polymorphisms (SNPs).
  - Most of the SNP variability in the human genome is scattered throughout the large part of the genome that is not part of a gene (intergenic regions) or located in noncoding (intronic) sequences within genes: Among 3 billion human nucleotides, 95% are introns, 5% are exons.
  - SNPs in exons can be classified as synonymous cSNP (c means coding) or non-synonymous cSNP → as explained in "toxicology", there are many enzymatic polymorphisms.
  - (e.g.) Naka I, Hikami K, Nakayama K, Koga M, Nishida N, Kimura R, Furusawa T, Natsuhara K, Yamauchi T, Nakazawa M, Ataka Y, Ishida T, Inaoka T, Iwamoto S, Matsumura Y, Ohtsuka R, Tsuchiya N, Ohashi J (2013) A functional SNP upstream of the beta-2 adrenergic receptor gene (ADRB2) is associated with obesity in Oceanic populations. *International Journal of Obesity*, 37: 1204-1210. https://dx.doi.org/10.1038%2Fijo.2012.206
- Other types of variability
  - Insertion or deletions of nucleotides (**indels**) in genes → When it causes a disease, it's referred as "mutation" rather than polymorphism
    - (e.g.) Kimura M, Tamam M, Soemantri A, Nakazawa M, Ataka Y, Ohtsuka R, Ishida T (2003) Distribution of a 27-bp deletion in the band 3 gene in South Pacific islanders. *Journal of Human Genetics*, 48: 642-645. https://doi.org/10.1007/s10038-003-0093-4
  - An entire gene is missing (deletion polymorphism; e.g. hGSTM1 gene exists in only 50%) or occurs more than once in the same genome (gene duplication, copy number variation [CNV])
  - An entire chromosome appears 3 copies (triploid): e.g. Down's syndrome is 21 trisomy.

Regulation of gene expression & epigenetics

- Transcription factors and promoter regulation of genes
  - Phenotype is determined by the small part of genome
  - The trigger to begin transcription is determined by specific sequence of DNA in the 5'-flanking region (promoter region, Fig. 7.2.)
  - Specific proteins (transcription factors) bind to promoter region, then initiate the process of transcription
    - Sometimes transcription factors need a small molecule (estrogen, testosterone, thyroid hormone) before moving to the nucleus of the cell to bind to the binding site on a gene. Such small molecule is "ligand".
    - Some kinds of environmental chemicals mimics ligand to intervene this transcription process. Those are called as "endocrine disruptors".
- Epigenetics
  - Methylation/accetylation of DNA is related with its epression, those are modified by external molecule (Figure 7.4).
  - Binding of microRNA (miRNA) to the 3'-terminal ends of mRNA inhibits transcription to decrease gene expression
  - e.g. Maternal diet changes skin color of offspring in mice (Figure 7.5).

Figure 7.4 and Figure 7.5

Thrifty Phenotype as an example of epigenetics

(Hales CN, Barker DJ (2001) The thrifty phenotype hypothesis. *Br. Med. Bull*. 60: 5-20. https://doi.org/10.1093/bmb/60.1.5)

Odds ratio of metabolic syndrome by birth weight (lb; 2.2lb=1kg) adjusted by adulthood BMI

Figure of hypothetical mechanism and graph to show odds ratio

Omics technologies

- The study of the genome → genomics
- The study of the transcriptome (mostly mRNA) → transcriptomics
- The study of the proteome (entire population of proteins within a cell or tissue) → proteomics
- The study of metabolome (all parts of a cell constituting complex metabolism) → metabolomics
- The study of epigenetic factors → epigenomics
- New computing approaches enabled to analyze huge datasets obtained from omics → All possible combinations or comparisons can be tested → Increase of type I error becomes problem, adjustment of p-values in multiple comparison is needed → FDR adjustment is applied. (cf.) LAMP (Limitless-Arity Multiple testing Procedure), see, https://doi.org/10.1073/pnas.1302233110

Gene-environment interaction

- Approaches
  - Garrod found alkaptonuria as genetic metabolic disorder. Bateson described aggregation of such metabolic disorders in family.
  - Single gene disorder is rare. Rather too complex, resulted from gene-environment interaction, diseases like type 2 DM and obesity are common.
    - Pima Indian living in Arizona shows much higher prevalence of obesity and type 2 DM than Caucasians there, but Pima Indian living in Mexico shows low prevalence of obesity and DM.
      See, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4418458/pdf/nihms657043.pdf
      https://www.youtube.com/watch?v=AwaHNy5cwdU
  - Genetic association study is widely conducted
- Examples
  - Drug responses: Primaquine causes severe hemolysis in people with low activitiy variant allele of G6PD gene → Needs of Tailor-Made Medicine
  - Dietary exposures: alcohol (interact with ADH/ALDH – low activity ALDH2*2 holder is "flusher"), mercury (interact with CPOX and COMT)
  - Occupational exposures: benzene (interact with CYP2E1 enzyme)
  - Environmental exposures: some kinds of pesticides (interact with PON1 enzyme)

Chapter 18. Pest Control and Pesticides

- Note: "Pest" in Japanese usually means a specific disease name of plague, but here "pest" has much wider sense.
- Key Concepts
  - Pests are plants, animals, or microorganisms that threaten human health
  - Each pest has specific biological and ecological characteristics
  - Pest control relies heavily on chemical agents
  - There are many different classes of pesticides
  - People are exposed to pesticides in many ways (incl. Residual pesticides in foods)
  - Pesticide regulation is complex and relies on federal and states laws (in USA)
  - Integrated Pest Management (IPM) is a strategy combining chemical and nonchemical methods

History of pest control

- Pests existed and were identified in ancient societies
- Efforts to control pests also have long history
  - Past control measures: chalk, plant extracts, mercury, arsenic, lead and other compounds, in addition to sacrifices, prayers, rituals and dancing
- Chemicals
  - Paris green (copper acetoarsenite) was the first insecticide widely used for agriculture
  - DDT was found in 1939, widely used during WWII
  - DDT-like chlorinated pesticides were developed
  - Public health and ecological researches revealed problems ranging from human toxicity to wildlife toxicity to ecosystem disruption → Rachel Carson's "Silent Spring" (1962) altered the public and policymakers to the risks associated with pesticide use
  - Damages caused by pesticides cost $12 billion in USA: Loss of natural pest predators, crop pollinators, honeybees, crops, wildlifes
- Today we are moving beyond exclusive reliance on pesticides to the combination of chemical and nonchemical methods (IPM)

Figures 18.1 and 18.2

Seven categories of public health pests, defined by USEPA

- Cockroaches: asthma, allergies, food contamination
- Body, head, and crab lice: skin irritations and rashes, louse-borne diseases (typhus, trench fever, relapsing fever)
- Mosquitoes: mosquito-borne diseases (malaria [*Anopheles*], yellow fever [*Culex*], dengue fever [*Aedes*], some kinds of encephalitis [mostly *Culex*])
- Rats and mice: rodent-borne diseases, contamination of food for human consumption
- Microorganisms (bacteria, viruses, protozoa): pathogen itself
- Reptiles and birds: reservoir host of zoonosis, physical injury
- Various mammals: reservoir host of zoonosis, physical injury

* Other pests include bedbugs, fleas, sand flies, termites, ticks, and so on. Recently SFTS (severe fever with thrombocytopenia syndrome) is known as an emerging disease, of which virus is transmitted by tick's bites,

Control for insect pests

- Insect repellent
  - Preventing bites from biting insects (mosquitoes, ticks, fleas, chiggers, biting flies)
  - It cannot prevent bites from stinging insects (bees, hornets, wasps)
  - It doesn't kill but deter them from settling on skin and cloths
  - DEET (10%-30%) is the most used one. Higher concentration means more long-lasting effects (10%=2hr, 24%=5hr). Higher than 30% gives no additional protection and risk of adverse side effects. Acute toxicity is very rare, but high-dose DEET may cause neurological effects (suggested by animal experiment)
  - Picaridin, lemon eukalyptus oil, 2% soybean oil are comparable with 10% DEET
  - Permethrin or DEET impregnated clothing is used for military wear
- Insecticides (a kind of pesticides)
  - Sprayed on crops, alongside residential streets, poured on gardens, squirted along baseboards and in basements, impregnated into clothing and bednets.
    - Permethrin or deltamethrin impregnated bednets contributed to malaria control. Recently LLINs (insecticides incorporated in the fibres of the net) like Olyset net [https://sumivector.com/mosquito-nets/olyset-net] and PermaNet [https://www.vestergaard.com/our-products/permanet] were developed and widely used for malaria control.
  - World annual consumption of pesticides is about 2 million tons, 45% is used in Europe, 25% is used in USA; In applied rate basis, usage of pesticides in Korea, Japan and India are 6.6, 12.0, and 0.5 kg/ha, respectively.

Pesticides classified by target or mode of action (1)

Target	Mode of action
Algicides	Control algae in lakes, canals, swimming pools, water tanks, etc.
Antifouling agents	Kill or repel organisms attaching to underwater surfaces
Antimicrobials	**Kill microorganisms (bacteria, virus)**
Attractants	Attracts pests (lure an insect or rodent to a trap, etc.)
Biocides	Kill microorganisms
Biopesticides	Pesticides derived from natural materials
Disinfectants and sanitizers	Kill or inactivate disease-producing microorganisms on inanimate objects (latrine, table, etc.)
Fumigants	Produce gas or vapor intended to destroy pests in buildings or soil
Fungicides	Kill fungi (blights, mildews, molds, rusts)
Herbicides	**Kill weeds and other plants growing in unwanted places**
Insecticides	**Kill insects and other arthropods**
Larvicides	**Kill larvae of insects**

← An example of well-known fumigants in Japan

Pesticides classified by target or mode of action (2)

Target	Mode of action
Microbial pesticides	**Microorganisms that kill, inhibit or outcompete pests**
Miticides (Acaricides)	Kill mites on plants and animals
Molluscicides	Kill snails and slugs
Nematicides	Kill nematodes
Ovicides	**Kill eggs of insects and mites**
Repellents	Repel pests (insects, birds, etc.)
Rodenticides	Control mice and other rodents (eg. strychnine)
Defoliants	Cause leaves or other foliage to drop from a plant, facilitate harvest
Desiccants	Promote drying of living tissues (for unwanted plant tops)
Insect growth regulators	Disrupt the molting, maturing from pupal to adult stage
Pheromones	Disrupt the mating behavior of insects
Plant growth regulators	Alter expected growth, flowering or reproduction of plants (excluding fertilizers and other nutrients)

Organophosphates (OPs)

- Developed in 19C, utility was found in 1932.
- Organophosphate pesticides are neurotoxin, inactivates acetylcholinesterase (regulating neurotransmitter acetylcholine) → Some of those can be used as nerve gas (VX gas in WWII, sarin in Tokyo subway attacks 1995), but major uses were insecticides like chlorpyrifos, diazinon, malathion, azinphos-methyl.
- Unlike persistent organochlorine pesticides [https://dx.doi.org/10.1515%2Fintox-2016-0012] such as DDT, OPs degrade naturally in the environment after several days
- Human exposure: unintentionally/intentionally, ingestion/inhalation
  - In USA, unintentional exposure with very low concentration is widespread: Eating freshly picked foods contaminated with trace pesticide residues, inhaling household dust contaminated with pesticide residue.
  - In Cambodia, vegetables sold in markets sometimes contain higher level of pesticide residue than maximum safe limit [https://ejfoundation.org/resources/downloads/death_in_small_doses.pdf].
  - In Ghana, some ready-to-eat vegetables contained higher level of OPs but were not considered as the cause of major public health problems [https://doi.org/10.1016/j.foodcont.2016.03.045] [https://doi.org/10.1016/j.fct.2008.09.049] [https://doi.org/10.1007/s10661-015-4471-0].
- Alternatives
  - Carbamates: Inactivates acetylcholinesterase, but lower affinity than OPs and non-persistent
  - OCs (organochlorines): Less acute toxicity, but persistent. Major source of POPs (persistent organic pollutants, including DDT, PCB, etc.).
  - Pyrethroid pesticides: Synthetic version of natural pyrethrin, more stable than pyrethrin in the environment and toxic to the nervous system, but less toxic than Ops.
  - Biopesticides: Lower mammalian toxicity, but more expensive. e.g. canola oil and baking soda

Herbicides

- Herbicides: The most widely used type of pesticide in the agriculture, to reduce the effort to eliminate unwanted weeds from the farm by the farmers.
- Top ten pesticides used (by weight) were mostly shared by herbicides, including glyphosate (Roundup by Monsant), atrazine, metolachlor, acetochlor, 2,4-D, pendimethalin
- Herbicides are also widely used in the home and garden, industrial, commercial and government: 2,4-D and glyphosate were most widely used active ingredients (USEPA, 2011).
- Combination of genetically modified (GM) crops can facilitate the use of herbicides like glyphosate-resistant crops with Roundup; A kind of integrated pesticide management (IPM)
  → Widespread and controversial practice (see, Chapter 19)

Pesticide regulation

- Pesticide policy and law make up a complicated patchwork, addressing different aspects of health, safety, and environment
- USA
  - The principal pesticide law is FIFRA (federal insecticide, fungicide and rodenticide act) [https://www.epa.gov/laws-regulations/summary-federal-insecticide-fungicide-and-rodenticide-act]. Major policies are:
    - Requires product "registration" prior to manufacture, sales or use
    - Requires toxicity data
    - Requires specific labeling [https://www.epa.gov/pesticide-labels]
    - Requires training of applicators
    - Restricts handling and uses
  - Another important law in USA is FFDCA (federal food, drug, and cosmetic act)
  - FQPA (food quality and protection act) of 1996 updated both FIFRA and FFDCA by mandating a single, health-based standard for all pesticides in all foods, based on "reasonable certainty of no harm"
  - For workers, WPS (worker protection standard), for wildlife, ESA (endangered species act) have been set.
- Japan
  - Agricultural Chemicals Regulation Act [https://www.acis.famic.go.jp/eng/hourei/]
  - Food Sanitation Law and Food Safety Basic Law [https://www.mhlw.go.jp/english/topics/foodsafety/positivelist060228/introduction.html]
- FAO and WHO establish MRLs (maximum residues limits), maximum levels of pesticide residue that food can contain and still be expected not to harm human health: Member states can use these MRLs to develop national regulations.

Integrated Pest Management (IPM)

- Definition
  - "A comprehensive approach to pest control that uses combined means to reduce the status of pests to tolerable levels while maintaining a quality environment" (Pedigo, 2002)
  - "IPM is a decision support system for the selection and use of pest control tactics, singly or harmoniously coordinated into a management strategy, based on cost/beneft analyses that take into account the interests of and impacts on producers, society, and the environment." (Kogan, 1998 https://entomology.rutgers.edu/graduate/docs/papers/Kogan.pdf)
- Management and cultural practices to control pests: Farmers and public health officials use various management and cultural practice to reduce pest populations or to make conditions less favorable for pests
  - Farmers: Planting crop when pest population is lower, using a cultivar more resistant to pests, using a plastic mulch to reduce weeds, conserve moisture
  - Public health officials: Avoid standing water to reduce mosquitoes, control garbage buildup to manage flies, recommend meticulous cleaning and waste management to reduce other nuisance pests
- Structural maintenance and monitoring are key to be sustainable
- The use of chemical pesticides should be seen as a last resort. When used, comparatively less harmful ones to health and the environment should be chosen

Chapter 19. Food systems, the environment and public health

- Key concepts
  - The food system, from initial inputs to production to distribution to consumer choices, is a complex system, best understood using a systems approach
  - **Green Revolution**, including the use of fertilizers, pesticides and machinery, and innovative crops, greatly altered methods of food production and increased output, with some adverse consequences
  - In USA, most food is produced and distributed using large-scale industrial methods
  - A healthy food system is defined as "health-promoting, sustainable, resilient, diverse, fair, economically balanced, and transparent"
  - Food safety is a traditional core function of environmental health, and practicing food safety is important for controlling both bacteriological and chemical contamination and spoilage **(However, the lecture of food safety is given later, not today)**

History of food system and now

- If the history of *Homo sapiens* were compressed into a single year,
  - Farming started in the evening of December 13
  - Industrial agriculture started in the morning of December 29
- Modern food system is extremely large and permeates many aspects of our lives.
- In USA, food production accounts for over half of land, 16% of energy, 80% of consumptive water use; 13% of GDP is accounted by food

Food system

- Food travels through the landscape via food supply chains of varying lengths: involving production, distribution, consumption, waste disposal.

Figure 19.1

Natural resources of industrial agriculture

- Soil: Healthy soils contain thriving ecosystems – up to a billion bacteria in each teaspoon – and are resilient to drought. Once eroded, reconstruction needs more than a century. Plowing, overgrazing, excessive fertilization degrade topsoil much faster than it can be replenished. FAO reports 25% of the world lands are severely degraded.
- Water: Agriculture is the world's biggest freshwater user. Livestock products use far more water than other agricultural activity. Much water is drawn from underground aquifer, which may be nonrenewable. Fertilizers and pesticides degrade water quality.
- Biodiversity: The existence of a variety of different species and organisms in an ecosystem is important for agriculture. Industrial agriculture is sometimes monoculture (large expanses of the same crop): About half of USA cropland is used to grow genetically uniform corn and soybeans. Very vulnerable to pest invations and plant diseases. (eg. Cavendish cultivar of banana shares about half of global banana production, which suffers from new Panama disease caused by a fungi)
- Energy: Much labor in agriculture is replaced by machinery, which consumes fossil fuels. About 7-10 calories of input energy is needed to produce 1 calory of food. Use of renewable energy including biomass power is encouraged.
- Climate: Stable climate is also a "resource". Global warming and disasters such as hurricane give damages to agriculture

Manufactured agricultural inputs

- Pesticides → See, previous slides
- Fertilizers: Traditionally farms had a mix of animals and crops, with the animal's manure serving as fertilizer for the crops. Once science discovered a way to fix atomospheric nitrogen to produce synthetic fertilizers (Haber-Bosch process), animal manure became non-essential. Since Green Revolution, crops take up only 30-50% of fertilizer nitrogen, 45% of phosphorus, then excess nutrients runs off the land and becomes **nutrient pollution** in marine ecosystems → causes eutrophication, dead zones, harmful algal blooms (toxins from HAB causes massive die-out of fish and neurotoxic disorders or chronic diseases in humans)
- Genetically engineered seeds: One of the most controversial technologies. GM corn and soybean seeds came on the market in 1996, but already account for vast majority of USA corn and soybean. Roundup-resistant crops or Bt crops can reduce overall amount of herbicide use. But roundup may be carcinogenic or cause birth defects, Bt gene may transfer to wild plants and cause ecological pollution, or pest insects gradually develop resistance against Bt.

Industrial food animal production (IFAP)

- In USA, more than 9 billion food animals are slaughtered every year.
- Nearly all of the meat, milk and eggs consumed in USA are produced in a system known as IFAP (industrial food animal production), which raises animals in CAFOs (concentrated animal feeding operations). IFAP model has been exported to many other countries including China, India and Brazil.
- CAFOs' biggest problem is routine use of antibiotics → antibiotic-resistant bacterial strains, which in turn may cause antibiotics resistant human diseases
- IFAP animal waste is commonly stored in large manure cesspits, then released to environment, resulted in water and air contamination

Figure 19.3