

TABLE 1

Genetic Epidemiology and Core Public Health Functions in the Continuum from Genes to Public Health

Step	Description of activities	Disease/gene examples
GENETIC TECHNOLOGY HUMAN GENOME PROJECT	Gene mapping and linkage studies in high risk families	50,000-100,000 genes such as BRCA1 in breast cancer
     V		
ASSESSMENT	<b>GENETIC EPIDEMIOLOGY</b>	ApoE E4 allele and Alzheimer's disease
     V		
POLICY DEVELOPMENT	When and how genetic tests are to be applied in public health programs	Screening for various genes
     V		
ASSURANCE	Development of public health genetic programs, evaluation of prevention effectiveness, quality assurance	Newborn screening for metabolic disorders; proficiency testing for newborn screening

**TABLE 2**

**Genetic Epidemiology and Assessment of the Role of Genetic Factors in Disease**

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Aspects	Examples
<u>I. Population studies</u>	
A. Prevalence of susceptibility alleles in various populations	Studies of the frequency of BRCA1 mutations in different ethnic groups
B. Determinants of mutations in various populations	Studies of risk factors for chromosomal anomalies such as Down syndrome
C. Association between genetic traits and diseases	Studies of ApoE-E4 allele in Alzheimer's disease in the population
<u>II. Family studies</u>	
A. Familial aggregation of diseases	Recurrence risks of birth defects after an affected pregnancy
B. Causes of familial aggregation of disease	Studies of genetic and environmental factors in the recurrence of various diseases
C. Establishing genetic modes of inheritance	Segregation and linkage analysis in families

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**TABLE 3**

**Gene-Environment Interaction Analysis in a Case-Control Study**

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Exposure	Suscep- tibility genotype	Cases	Controls	Odds Ratio
(1=present, 0=absent)				
0	0	A <sub>00</sub>	B <sub>00</sub>	OR <sub>00</sub> = 1.0
0	1	A <sub>01</sub>	B <sub>01</sub>	OR <sub>01</sub> = A <sub>01</sub> B <sub>00</sub> / A <sub>00</sub> B <sub>01</sub>
1	0	A <sub>10</sub>	B <sub>10</sub>	OR <sub>10</sub> = A <sub>10</sub> B <sub>00</sub> / A <sub>00</sub> B <sub>10</sub>
1	1	A <sub>11</sub>	B <sub>11</sub>	OR <sub>11</sub> = A <sub>11</sub> B <sub>00</sub> / A <sub>00</sub> B <sub>11</sub>

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Case-only odds ratio  $OR_{ca} = A_{11}A_{00} / A_{10}A_{01} = (OR_{11} / OR_{10}OR_{01})OR_{co}$

Where  $OR_{co} = B_{11}B_{00} / B_{10}B_{01}$  (control-only odds ratio)

TABLE 4

Case-Control Analysis of the Interaction Between Maternal Cigarette Smoking, Transforming Growth Factor Alpha Polymorphism, and the risk for cleft palate. Adapted from Hwang et al. (11)

Smoking	TaqI Polymorphism	Cases	Controls	Odds Ratio	95% C.I.
-	-	36	167	1.0	Referent
-	+	7	34	1.0	0.3-2.4
+	-	13	69	0.9	0.4-1.8
+	+	13	11	5.5	2.1-14.6

Crude odds ratios are presented.

Odds ratio based on a case-only study is 5.1 (95% C.I. 1.5-18.5)  
 $(13 * 36) / (13 * 7)$

TABLE 5

Characteristics of Nontraditional Case-Only Studies

Feature	Case-Only	Case-Parental Control	Affected Relative-pair
Study Subjects	Cases	Cases and their parents	Second case in family, proband, and parents
'Controls'	None	Expected genotype distribution based on parental genotypes	Expected distribution of alleles with Mendelian transmission
Assessment	Departure from multiplicative relation between exposure and genotype	Association between genotype and disease  Also departure from multiplicative relation	Linkage between locus and disease  Also departure from multiplicative relation
Assumptions	Independence between genotype and exposure	Mendelian transmission	Mendelian transmission
Strengths & limitations	Simple. Cannot assess effects of exposure or genotype. Linkage disequilibrium	Requires one or both parents. Cannot assess exposure effects. Linkage disequilibrium	Need families with 2 or more cases. Cannot assess exposure Cannot assess specific

TABLE 6

**Gene-Environment Interaction Analysis in the Context of a Case-Parental Control Study: Analysis of Nontransmitted Alleles**

		Susceptibility genotype	
Exposure: Absent		Cases	
		Present	Absent
Parental non-transmitted alleles	Present	$T_0$	$U_0$
	Absent	$V_0$	$W_0$
Odds Ratio (among unexposed)		1	$U_0/V_0$
Exposure: Present		Cases	
		Present	Absent
Parental non-trans-	Present	$T_1$	$U_1$

mitted alleles

Absent

$V_1$

$W_1$

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Odds

1

$U_1/V_1$

Ratio (among  
exposed)

**TABLE 7**

**Gene-Environment Interaction Analysis in the Context of an Affected Sib-Pair Study**

No. Alleles ibd with	Unexposed case	Exposed case	Expected	Odds Ratio (unexposed)	Odds Ratio (exposed)
0	$A_{00}$	$A_{01}$	0.25	1.0	1.0
1	$A_{10}$	$A_{11}$	0.50	$A_{10}/2A_{00}$	$A_{11}/2A_{01}$
2	$A_{20}$	$A_{21}$	0.25	$A_{20}/A_{00}$	$A_{21}/A_{01}$

**TABLE 8**

**Incorporating a Familial Analysis of Reconstructed Cohorts into a Case-Control Study**

Disease in a Relative	Disease in Index Persons	
	Case	Control
Yes	$A_1$	$A_0$
No	$B_1$	$B_0$
Total	$N_1$	$N_0$

Total of case relatives is  $N_1$  and control relatives  $N_0$ .  
Disease proportion in case relatives  $A_1/N_1$   
Disease proportion in control relatives  $A_0/N_0$   
Risk ratio  $(A_1/N_1)/(A_0/N_0)$

**TABLE 9**

**Linkage analysis in an Epidemiologic Study Design**

Alleles ibd w probands	Cohort study		Case-control study		
	Disease Risk	Risk ratio	Recurrent cases	Controls	Odds ratio
0	$R_0$	1.0	$A_0$	$B_0$	1.0
1	$R_1$	$RR_1$	$A_1$	$B_1$	$A_1B_0/A_0B_1$
2	$R_2$	$RR_2$	$A_2$	$B_2$	$A_2B_0/A_0B_2$