Agenda
CIAHD Monthly Research Meeting
SPH I, Room 4645
January 29, 2009
3:00 – 5:00pm (Eastern)

I. Administrative Items — Ana Diez Roux, Center PI — (20 minutes)
   a. CIAHD at JHS Symposium
   b. CIAHD Summer Internship

II. Presentations — (60 minutes)

Research Project 1, Presenter – Sharon Kardia "Genetic and Social Factors in Blood Pressure Control in Hypertensives"

2008/2009 Funded Pilot, PI - Yan Sun "A Comparative Study of the Prevalence and Predictors of Hypertension in Chinese living in China vs. the United States"

III. Meeting Wrap-up/Action Items — (10 minutes)

Center for Integrative Approaches to Health Disparities

Project 2

January 29, 2009

Candidate Gene Studies

- Based on selection of genes with known/putative biological function
- Functional role may predispose to disease or phenotype of interest
- Similar to traditional epidemiological approaches
  - Test hypothesis between exposure and disease
  - "exposure" – genotype at a given locus

Single Nucleotide Polymorphisms

- DNA sequence variation
  - Single nucleotide (A,T,C, or G) in genome sequence is altered
- Variation that occurs in at least 1% of population
- Make up ~ 90% of human genetic variation
- Do not cause disease
- May help determine the likelihood that someone develops disease

Candidate Gene Studies in GENOA

- ~ 260 genes selected
  - Chosen for known/potential involvement with hypertension
  - Pathways include:
    - Coagulation, lipid, metabolic, inflammation, blood-pressure regulation, vascular wall
- ~ 1950 SNPs typed
  - tagSNP selection used to cover most of the variation in selected genes
- SNPs typed in
  - ~ 1500 individuals in Rochester, MN
  - ~ 1800 individuals in Jackson, MS

Candidate Gene Summary

Chromosome	Local Loci									
1	ADPRHL2	AGT	AGTRAP	CFH	CKS1B	CLCN6	COL16A1	COL8A2	CRP	ECE1
	F13B	F3	F5	FABP3	FNDC5	GJA4	HTR6	IL10	IL22RA1	IL28RA
	LDLRAP1	MTHFR	MTR	NPPA	NPPB	PCSK9	PLA2G2E	PTAFR	S100PBP	SELE
	SELP	SERPINC1	SHC1	TMCO4	TNFRSF1B	TNFSF4	USF1	USP24	VCAM1	
2	ACCN4	ADD2	ADRA2B	ALMS1	APOB	ATP6V1B1	AUP1	CAPN10	DCTN1	DQX1
	FLJ12788	GCG	GLS	GPR35	GPR55	HMGA1L4	HSPD1	HTR2B	IL1A	IL1B
	IRS1	KCNE4	KCNJ13	LOC130951	LRP2	MGC10995	MGC22014	MOBK1B	MTHFD2	NMUR1
	NPPC	PRSS25	SCN7A	SLC19A3	SLC20A1	SLC4A3	SLC4A5	SLC9A1	SLC9A2	STAMBP
	STAT1	TFPI	VAMP5	VAMP8						
3	ADIPOQ	AGTR1	CCR3	CX3CR1	GATA2	GHRL	SCAP	SLC2A2	TNFSF10	
4	ADD1	EDNRA	FABP2	FGB	HTRA3	PF4	PPBP	SOD3	SPP1	
5	ADRB2	F12	IL13	IL4	IL9	PART1	PDE4D	PIK3R1	THBS4	
6	AGER	ALDH5A1	CUC1	CMAH	COL19A1	DEK	EDN1	F13A1	GABBR1	HFE
	HLA-A	HLA-DOA	HTR1B	IFNGR1	IL17	KAAG1	KCNK16	KCNK17	KCNK5	LOC401237
	LPA	LTA	MRS2L	NUP153	OPRM1	PLA2G7	PLG	PRL	RDS	RHAG
	ROS1	SLC17A1	SLC17A2	SLC17A3	SLC17A4	SLC22A3	SRF	TDRD6	TNF	TTRAP
	VEGF	WIAF1959	WIAF614	WIAF98						

Immunoregulation and inflammatory markers
Neurotransmitter regulation
Lipid metabolism
Oxidative stress pathway

Candidate Gene Summary

Chromosome	Local Loci									
7	FGL2	HGF	HSPB1	IL6	KIAA1505	LEP	NOS3	PON1	PON2	PRKAR2B
	SERPINE1									
8	CYP11B1	CYP11B2	EPHX2	HTRA4	LPL	PLEKHA2	SLC25A32	TMD03	WDSOF1	
9	ABCA1	PAPPA	PTGS1	TLR4						
10	ADRB1	HTRA1	IL15RA	ITGA8						
11	ADM	APOA4	APOA5	APOC3	F2	IL18	KCNJ11	MMP1	MMP3	SAA1
	TEX12	ZNF259								
12	ARHGAP9	C3AR1	DDIT3	GNB3	HAL	KITLG	LTA4H	MARS	NECAP1	RAN
	SCNN1A	TAS2R50	TNFRSF1A	VWF						
13	ALC05AP	EDNRB	F10	F7	GPC6					
14	BDKRB2	LOC730109	PSMA6	TGFB3						
15	CAPN3	GRP58	LIPC	ONECUT1	PLCB2	PLIN				
16	AYTL1	CETP	CYBA	MMP2	SLC12A3					
17	ABCA6	ACE	ALOX12	LOC728478	CCL2	CCL5	GP1BA	ITGB3	MGC71993	MPO
	NOS2A	SLC25A11								
19	APOE	AXL	CARM1	CLEC11A	DNMT1	GAMT	HNRPUL1	ICAM1	JunD	LDLR
	PLAUR	RETN								
20	AVP	MMP9	PROCR	THBD						
21	IFNAR2	IFNGR2								
X	ACE2	AGTR2	GABRA3	SYN1	TIMP1					

Immunoregulation and inflammatory markers
Oxidative stress pathway
Lipid metabolism

NCBI Entrez Gene

- Searchable database of genes
  - Search by:
    - Gene symbol (CRP)
    - Official gene name (C-reactive protein)
    - GeneID (1401)
- http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene

Genome-Wide Association Studies

- Examination of variation across genome
- Increased potential for:
  - detecting variations of small but significant effects on disease susceptibility
  - increasing understanding of biological processes and disease etiologies
  - contributing to the promise of personalized medicine

Follow-up to GWAS Studies

- Fine mapping of notable / significant regions
- Functional determination of variants
- Pathway exploration

GWAS Summary

Chromosome	# of Affy SNPs	Mean Distance of Affy SNPs	# of Imputed SNPs	Mean Distance of Imputed SNPs
1	71554	3447	191554	1274
2	74171	3272	220833	1099
3	60887	3273	174356	1143
4	56198	3401	163157	1172
5	56625	3188	168144	1074
6	56470	3022	182381	936
7	47232	3360	142232	1108
8	48782	2996	147483	993
9	41574	3371	122112	1148
10	48345	2796	138402	978
11	44701	3004	130069	1032
12	42722	3096	124860	1059
13	34400	2796	104120	924
14	28179	3090	83936	1044
15	26161	3130	72300	1135
16	27806	3189	71550	1239
17	20733	3793	58455	1345
18	26631	2858	76812	991
19	11968	5313	37045	1716
20	22910	2723	63408	984
21	12621	2930	33863	1094
22	11570	3037	33815	1019
	872242		2543887	

Affy: Affymetrix 6 http://www.affymetrix.com/index.affx

Additional Information Resources

- **National Center for Biotechnology Information**
  - http://www.ncbi.nlm.nih.gov/
- **National Human Genome Research Institute**
  - http://www.genome.gov/20019523
- **Human Genome Project**
  - http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml

Center for Integrative Approaches to Health Disparity (CIAHD) Pilot Study 2008-2009

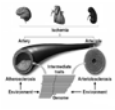
A Comparative Study of the Prevalence and Predictors of Hypertension in Chinese living in China vs. living in the United States

Yan V. Sun, Ph.D.
Department of Epidemiology
University of Michigan

January 29th, 2009

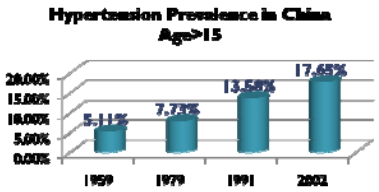
Common Diseases – Gene or Environment?

$$Y = G + E$$


China NHANES 2002

Hypertension in China



165 (177) million adult Chinese are hypertensives in 2002

Risk Factors of Hypertension (Tianjin 2002, n=1285)

	Z score	p-value
Age	9.574	<0.0001
Gender	3.426	0.0006
Education	2.321	0.0203
Income	1.485	0.138
BMI	8.284	<0.0001

Jiang et.al. 2002

4

Tianjin

Tianjin is one of the four municipalities that have provincial-level status. Both typical urban and rural areas exist in Tianjin. There are over 11 million permanent residents living in Tianjin.

5

Hypertension Risks in MESA Chinese

	Chinese	
	HTN+ *n* = 311	**HTN− *n* = 492**
Age (y)*	67.1 (9.5)	60.3‡ (10.0)
% Male	45	51
BMI (kg/m^2)*	24.8 (3.5)	23.5‡ (3.1)
Waist circumference (cm)*	90.1 (9.9)	85.2‡ (9.5)
% DM	19	11‖
% Smoking (current)	5	6
% High school education	71	78
Total household income (in thousands)*†	33.5 (32.5)	43.1§ (36.9)

‡ *P* < .0001; § *P* < .001; ‖ *P* < .01 Kramer H. *AJH* 2004

6

Tianjin vs. MESA Chinese

Sex-specific hypertension prevalence in Tianjin, China

Age	Male		Female	
	N	Hypertensive (%)	N	Hypertensive(%)
15-29	185	29 (15.7%)	260	16 (6.2%)
30-44	274	91 (33.2%)	361	56 (15.5%)
45-54	250	132 (52.8%)	303	114 (37.6%)
55+	329	211 (64.1%)	388	234 (60.3%)
Total	1038	463 (44.6%)	1312	420 (37.6%)

Jiang et.al. 2002

Sex-specific hypertension prevalence in MESA Chinese.

Age	Male		Female	
	N	Hypertensive (%)	N	Hypertensive (%)
45-54	111	19 (17.1%)	113	21 (18.6%)
55+	279	118(42.3%)	300	143(47.7%)
Total	390	137(35.1%)	413	164(39.7%)

Aims

$$Y = G + E$$

Given that almost all of the Chinese Americans in MESA study are the first generation of the immigrants, the genetic effects are unlikely the cause of the different hypertension prevalence between Chinese living in Tianjin, China and US.

Aim1: To identify the risk factors of hypertension in Chinese ethnicity, we will test for the effects associated with hypertension, as well as SBP and DBP in Tianjin and MESA Chinese separately.

Aims

Aim 2: We will explore the cause of the RF (e.g. Sex) differences if it is present by

a) Investigating the extent to which differences in the distribution of risk factors is associated with RF difference in hypertension and BP measurements;

Confounding

b) Examining whether the risk factors have interaction effects.

E x RF Interaction

Statistical Models

Confounding

$$y_i = \beta_0 + \beta_1 \cdot Age_i + \beta_2 \cdot U_i + \beta_3 \cdot Sex_i + e_i$$

Interaction

$$y_i = \beta_0 + \beta_1 \cdot Age_i + \beta_2 \cdot U_i + \beta_3 \cdot Sex_i + \beta_4 \cdot U_i \times Sex_i + e_i$$

Potential Risk Factors

- Age
- BMI, WHR
- Smoking
- Alcohol Consumption
- Physical Activity
- Cholesterol, HDL, LDL, Triglyceride
- Education
- Income

Challenges

- Comparability
  - Sample (Age, disease history)
  - BP Measurement
    - Mercury vs. Dinamap PRO 100 (Ni *et.al.*2006)
  - Income and Education
    - Derived variable based on distribution
  - Urban vs. Rural Areas
- Interpretation
  - Confounding
- Follow up

Data Sets

	HTN Prevalence[a] (Age≥45)		
	Total	Male	Female
MESA Chinese (N=803)	37.5%	35.1%	39.7%
Tianjin Urban[b] (N=739)	49.8%	51.2%	48.7%
Tianjin Rural[b] (N=604)	55.6%	61.1%	50.0%

[a] : JNC VI definition – SBP≥140 or DBP≥90 or taking anti-hypertensive medication.

[b] : Han Chinese Only.

Preliminary Results

MESA Chinese

Outcome=HTN			Model 1 - Unadjusted			Model 2 - Age adjusted			Model 3 - Age BMI adjusted		
	N	Mean±SD	Beta	Beta_SE	P-value	Beta	Beta_SE	P-value	Beta	Beta_SE	P-value
Age	803	62.35±10.33	0.074	0.008	2.10E-20	NA			NA		
BMI	803	23.99±3.30	0.113	0.023	8.94E-07	0.140	0.025	1.66E-08	NA		
WHR	803	0.917±0.067	7.856	1.202	6.35E-11	5.592	1.257	8.69E-06	2.575	1.453	0.076
Cholesterol	802	192.6±31.80	0.000	0.002	0.872	0.001	0.002	0.640	0.002	0.002	0.382
HDL	802	49.52±12.71	-0.011	0.006	0.069	-0.016	0.006	0.012	-0.004	0.007	0.510
LDL	789	115.1±28.97	-0.002	0.003	0.353	-0.001	0.003	0.840	0.000	0.003	0.914
logTriglyceride	802	4.824±0.512	0.506	0.145	4.93E-04	0.609	0.156	9.45E-05	0.406	0.163	0.013
Sex	803	Male 48.6%	-0.196	0.146	0.180	-0.228	0.156	0.144	-0.245	0.159	0.124

Preliminary Results

Tianjin Urban (Age ≥ 45)

Outcome=HTN			Model 1 - Unadjusted			Model 2 - Age adjusted		
	N	Mean±SD	Beta	Beta_SE	P-value	Beta	Beta_SE	P-value
Age	739		0.044	0.007	0.000			
BMI	739		0.158	0.023	0.000	0.163	0.023	0.000
WHR								
Cholesterol								
HDL								
LDL								
logTriglyceride								
Sex	739	Male 44.1%	-0.102	0.148	0.49	-0.071	0.152	0.642

Tianjin Urban (45 > Age ≥ 18)

	Normal	Hypertensive	Total
Male	88	44	132
Female	204	25	229
Total	292	69	361

X-squared = 214.3019, df = 3, p-value < 2.2e-16

Preliminary Results

Tianjin Rural (Age ≥ 45)

Outcome=HTN			Model 1 - Unadjusted			Model 2 - Age adjusted		
	N	Mean±SD	Beta	Beta_SE	P-value	Beta	Beta_SE	P-value
Age			0.084	0.011	0.000			
BMI			0.072	0.022	0.001	0.077	0.023	0.001
WHR								
Cholesterol								
HDL								
LDL								
logTriglyceride								
Sex	604	Male 50.7%	-0.452	0.165	0.006	-0.465	0.174	0.008

Challenges

- Comparability
  - Sample (Age, disease history)
  - BP Measurement
    - Mercury vs. Dinamap PRO 100 (Ni *et.al.*2006)
  - Income and Education
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Two Lives of Data Analyst