A Role for Genomics in Addressing Health Disparities?

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Discourse on precision medicine, genomics, and health disparities

“give everyone the best chance at good health”
(Collins & Varmus NEJM 2015;372:793-5)

“improve outcomes for communities with disparities in health”
(Flyer for community engagement with AIAN communities)

“understand the complex interplay that creates health disparities”
(Bustamante et al Nature 2011;475:163-5)
Social conditions as fundamental causes of disease

Disadvantage creates conditions that put people “at risk of risks”

Influencing

- Multiple risk factors
- Multiple diseases

...and maintaining an association with disease, even when intervening mechanisms change

Link & Phelan J Health Soc Behav 1995(Extra):80-94
Survival by race in childhood acute lymphoblastic leukemia (ALL)

Lower 5 year survival for AA, NA and Hispanic compared to white children (p<0.001-0.002)

Incidence of childhood acute lymphoblastic leukemia (ALL)

Cases per million person years

Lim et al Cancer 2014; 120:955-62
Genetic contributors to disease risk

- **5 genes associated with ALL risk** (involved in lymphoid development, cell cycle control or tumor suppression)

- **Differential prevalence of risk variants** in 2 genes (lower in African Americans) likely contributes to racial difference in incidence

Lim et al Cancer 2014; 120:955-62
Hu et al JNCI 2013:733-741
Pui et al JAMA 2003; 290:2001
Another difference

- **Higher rate of poor prognostic indicators** seen in black children in US and Africa in some studies – e.g.:
  - High leukocyte count
  - Unfavorable T-cell immunophenotype
  - Chromosomal translocation t(1:19) with E2A-PBX1 fusion
  - Also, less likely to have hyperdiploid blast cells

- Could population genetic differences contribute? Or environmental exposures?

Results of therapy for ALL in Black and White children - St. Jude

Event-free survival

Pui et al JAMA 2003; 290:2001
Type 2 diabetes

- Accounts for 90-95% of diabetes
- >100 gene variants contribute to risk, with small additive effects
- In studies of ancestral groups:
  - Differences in variant prevalence
  - Some variants found exclusively or predominantly in specific groups
Could genetics account for the high rate of diabetes in the Arizona Pima?

Study of two Pima populations

- Located in Arizona, US and Sierra Madre mountains of Mexico
- Share common ancestry distinct from other Native American groups, with bootstrap value of 95% (947/1000)

Schulz et al. Diabetes Care 2016;29:1866-77
Age-adjusted prevalence (±95% CIs) of diabetes in non-Pima Mexicans, Mexican Pima Indians, and U.S. Pima Indians.

Leslie O. Schulz et al. Dia Care 2006;29:1866-1871
Other differences between the two Pima Indian populations

- Physical activity
  - 2.5-fold↑ for men, 7.0-fold↑ for women among Mexican Pima

- Obesity
  - 10-fold↑ for men, 3.0-fold↑ for women among US Pima

Schulz et al. Diabetes Care 2016;29:1866-77
How did the Pima lifestyle change with western settlement?

- Pima agricultural economy disrupted by diversion of water to white settlements
  - Loss of healthy traditional foods
  - Poverty
- Surplus commodities (high in simple carbohydrates and processed food) introduced as dietary mainstays
- Communities experienced cultural loss, stigma and discrimination

Age-adjusted prevalence (±95% CIs) of diabetes in non-Pima Mexicans, Mexican Pima Indians, and U.S. Pima Indians.
**APOL1 & kidney disease**

African Americans experience a disproportionate burden of chronic (CKD) and end-stage kidney disease (ESKD)

Risk variants in the APOL1 gene contribute to increased risk

- Risk genotype (two copies of a risk variant) present in 13% of African Americans
- Penetrance estimated at 20%
### Incidence of albuminuria (indicator of CKD) in the Cardia cohort

<table>
<thead>
<tr>
<th></th>
<th>White (N=1651)</th>
<th>Low risk Black (N=1090)</th>
<th>High risk Black (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1651</td>
<td>1090</td>
<td>152</td>
</tr>
<tr>
<td><strong>Albuminuria (per 1000 PY)</strong></td>
<td>3.9</td>
<td>7.8</td>
<td>15.6</td>
</tr>
<tr>
<td><strong>Relative risk</strong></td>
<td>--</td>
<td>2.32</td>
<td>5.71</td>
</tr>
<tr>
<td><strong>Corrected (smoking, BP, BMI, DM, SES)</strong></td>
<td>--</td>
<td>1.21</td>
<td>3.50</td>
</tr>
</tbody>
</table>

Peralta et al. JASN 2016; 27:888-93
Kidney decline by race and \textit{APOL1}

Peralta et al. JASN 2016; 27:888-93
Placing genomics in context

Genomics may:
- explain some population differences in disease incidence - sometimes aligned with outcome disparity, sometimes not

BUT
- Studied in isolation, may obscure far more important social determinants of health
- In so doing, may stigmatize disadvantaged populations and slow progress toward addressing health disparities

West et al JAMA 2017;317:1831-2
Sankar et al. JAMA. 2004;291:2985-9