Genome wide association study in Tehran cardio-metabolic genetic study could promotes genetic of obesity in Iran

Dr M. Daneshpour
Associate Prof, PhD, Cellular and Molecular Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: daneshpour@sbmu.ac.ir
Some challenges in genetic of obesity

• Is The Cure For Obesity Written In Our Genes?

Genetic Testing for Obesity: Implications and Challenges

Mary Segal
Human Genome and Single Nucleotide Polymorphisms (SNPs)

- 23 chromosome pairs
- 3 billion bases
- A single nucleotide change between pairs of chromosomes
- E.g.

  Haplotype1: AAGGGATCCAC
  Haplotype2: AAGGAATCCAC
Association Study in Case Control Samples

SNP1  SNP2  SNP3  SNP4  SNP5  Disease

CAGATCGCTG GATGAAATCGCATC
CGGATTGCTG CATGGATCGCATC
CAGATCGCTG GATGAAATCCCATC
CGGATTGCTG CATGGATCCCATC
CGGATTGCTG CATGGATCCCATC
Using SNPs to Track Predisposition to Disease

DNA from different individuals sequenced
Variation at a single nucleotide
Some individuals will have one version of the SNP, some the other

Sample with disease
Normal population

A higher than expected incidence in a disease group suggests SNP is associated with a disease (or SNP is protective)
In a population, a certain percentage will have one version, the rest the other
Genetic Spectrum of Complex Diseases

Manolio et al. 2009 Nature 461, 747-753
Genetic Spectrum of Complex Diseases

- Linkage
  - Few examples of high-effect common variants influencing common disease
- Rare alleles causing Mendelian disease
- Low-frequency variants with intermediate effect
- Common variants implicated in common disease by GWA
- Rare variants of small effect very hard to identify by genetic means
- Very rare
- Rare
- Low frequency
- Common

Effect size

- High
- Intermediate
- Modest
- Low

Allele frequency

- Very rare
- Rare
- Low frequency
- Common

Sequencing

GWAS
Genetic of cardiometabolic risk factors
Obesity could be classified into three subgroups:

• Monogenic
• Syndromic
• Polygenic or Common obesity
List of genes responsible for **monogenic obesity**: Autosomal recessive form of obesity

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Locus mutated</th>
<th>Encoded proteins</th>
<th>Usual physiological functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>LEP</em></td>
<td>Leptin (LEP)</td>
<td>Protein hormone produced by adipocytes and regulates eating behaviour</td>
</tr>
<tr>
<td>2.</td>
<td><em>LEPR</em></td>
<td>Leptin receptor (LEPR) in hypothalamus</td>
<td>Binds leptin and activates the synthesis of pro-opiomelanocortin (POMC)</td>
</tr>
<tr>
<td>3.</td>
<td><em>POMC</em></td>
<td>Pro-opiomelanocortin (POMC)</td>
<td>Precursor protein α-melanocyte stimulating hormone (α-MSH) along with other protein hormones</td>
</tr>
<tr>
<td>4.</td>
<td><em>PC 1</em></td>
<td>Prohormone convertase-1 (PC 1)</td>
<td>Catalyzes post-translational cleavage of POMC into α-MSH</td>
</tr>
<tr>
<td>5.</td>
<td><em>MC4R</em></td>
<td>Melanocortin-4 receptor (MC4R)</td>
<td>Binds of MC4R to α-MSH receptor, expressed in hypothalamus to activate anorexigenic signals</td>
</tr>
</tbody>
</table>
List of syndromic obesity in humans: Autosomal or X-linked

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Syndrome</th>
<th>Symptoms</th>
<th>Locus</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Prader-Willi syndrome (PWS)</td>
<td>Short physique with psychological defects, hypotonia and hypogonadism.</td>
<td>15q11.2-q12</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>Albright’s hereditary osteodystrophy (AHO)</td>
<td>Short physique with skeletal defects and defective olfaction</td>
<td>20q13.2</td>
<td>GNAS1</td>
</tr>
<tr>
<td>3</td>
<td>Fragile X syndrome</td>
<td>Psychological and speech defects with macro-orchidism</td>
<td>Xq27.3</td>
<td>FMR1</td>
</tr>
<tr>
<td>4</td>
<td>Ulnar-mammary syndrome</td>
<td>Postponed puberty with imperfect ulnar and hypoplastic nipples</td>
<td>12q24.1</td>
<td>TBX3</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Bardet-Biedl syndrome</td>
<td>Psychological and renal defects with retinal dystrophy and hypogonadism</td>
<td>11q13 (BB1)</td>
<td>BB1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16q21 (BB2)</td>
<td>BB2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15q22 (BB4)</td>
<td>BB3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20p12 (BB6)</td>
<td>BB6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALMS1</td>
</tr>
<tr>
<td>6</td>
<td>Alstrom syndrome</td>
<td>Retinal dystrophy with neurosensory deafness and diabetes</td>
<td>2p13</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Cohen syndrome</td>
<td>Prominent central incisors with ophthalmopathy, and macrocephaly</td>
<td>8q22</td>
<td></td>
</tr>
<tr>
<td>X-linked</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Böjesen-Forsman-Lehmann syndrome</td>
<td>Psychological defects with large pinna and hypogonadism</td>
<td>Xq26</td>
<td>FHFS</td>
</tr>
<tr>
<td>9</td>
<td>MEHMO syndrome</td>
<td>Psychological defects with epilepsy, hypogonadism, macrocephaly</td>
<td>Xp22.13</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Simpson-Golabi-Behmel, Type 2</td>
<td>Skeletal and visceral abnormalities</td>
<td>Xp22</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Wilson-Turner syndrome</td>
<td>Psychological defects with tapering fingers, and gynecomastia</td>
<td>Xp21.2</td>
<td></td>
</tr>
</tbody>
</table>
### List of genetic modifications (SNPs) showing polygenic effects on body weight in terms of BMI in humans

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Single nucleotide polymorphism (SNP)</th>
<th>Chromosome no.</th>
<th>Locus</th>
<th>Adjacent gene</th>
<th>Sample size</th>
<th>Allelic frequency</th>
<th>BMI outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>rs2115752</td>
<td>1p11</td>
<td>72,524,461</td>
<td>NEGR1</td>
<td>325,877</td>
<td>62% (A)</td>
<td>+0.10 kg/m² per A allele</td>
<td>61</td>
</tr>
<tr>
<td>2.</td>
<td>rs23140971</td>
<td>1q22</td>
<td>72,537,704</td>
<td></td>
<td></td>
<td>58% (A)</td>
<td>+0.10 kg/m² per A allele</td>
<td>61</td>
</tr>
<tr>
<td>3.</td>
<td>rs10913456</td>
<td>1q21</td>
<td>176,380,142</td>
<td>SECK1B, RASAL2</td>
<td>25,344</td>
<td>20% (A)</td>
<td>+0.20 kg/m² per C allele</td>
<td>61</td>
</tr>
<tr>
<td>4.</td>
<td>rs6548238</td>
<td>2p3</td>
<td>629,905</td>
<td>TMEG1B</td>
<td>32,387</td>
<td>84% (C)</td>
<td>+0.26 kg/m² per C allele</td>
<td>61</td>
</tr>
<tr>
<td>5.</td>
<td>rs7561517</td>
<td>3p11</td>
<td>634,953</td>
<td></td>
<td>25,344</td>
<td>84% (G)</td>
<td>+0.70 kg/m² per A allele</td>
<td>61</td>
</tr>
<tr>
<td>6.</td>
<td>rs7647580</td>
<td>4q31</td>
<td>187,361,984</td>
<td>SPS601, ETP51, DGK1</td>
<td>25,344</td>
<td>77% (G)</td>
<td>+0.54 kg/m² per C allele</td>
<td>62</td>
</tr>
<tr>
<td>7.</td>
<td>rs10938397</td>
<td>4p13</td>
<td>45,023,455</td>
<td>GNPDA2</td>
<td>32,387</td>
<td>48% (G)</td>
<td>+0.19 kg/m² per G allele</td>
<td>61</td>
</tr>
<tr>
<td>8.</td>
<td>rs4712052</td>
<td>6p22.2-p21.1</td>
<td>22,186,593</td>
<td>PRL</td>
<td>2,790</td>
<td>41% (A)</td>
<td>+0.03 kg/m² per A allele in children</td>
<td>63</td>
</tr>
<tr>
<td>9.</td>
<td>rs10588501</td>
<td>1p32</td>
<td>18,139,256</td>
<td>PTF1</td>
<td>2,790</td>
<td>85% (C)</td>
<td>+0.14 kg/m² per C allele in children</td>
<td>63</td>
</tr>
<tr>
<td>10.</td>
<td>rs6261 (V60Ms)</td>
<td>1p14</td>
<td>76,636,902</td>
<td>BDNF</td>
<td>25,344</td>
<td>80% (G)</td>
<td>+0.67 kg/m² per A allele in children</td>
<td>62</td>
</tr>
<tr>
<td>11.</td>
<td>rs1058679</td>
<td>1q21.12</td>
<td>47,585,695</td>
<td>MTCH1</td>
<td>32,387</td>
<td>34% (A)</td>
<td>+0.19 kg/m² per A allele in children</td>
<td>61</td>
</tr>
<tr>
<td>12.</td>
<td>rs138803</td>
<td>1q32</td>
<td>48,533,735</td>
<td>BCIN1D1A, PAM2</td>
<td>25,344</td>
<td>37% (A)</td>
<td>+0.34 kg/m² per A allele in children</td>
<td>62</td>
</tr>
<tr>
<td>13.</td>
<td>rs749551</td>
<td>16p12.1</td>
<td>28,790,742</td>
<td>SICT1</td>
<td>32,387</td>
<td>41% (G)</td>
<td>+0.15 kg/m² per G allele</td>
<td>61</td>
</tr>
<tr>
<td>14.</td>
<td>rs749665</td>
<td>16p12.1</td>
<td>28,790,742</td>
<td>ATPA1</td>
<td>25,344</td>
<td>44% (G)</td>
<td>+0.65 kg/m² per C allele</td>
<td>62</td>
</tr>
<tr>
<td>15.</td>
<td>rs5809513</td>
<td>16q22.2</td>
<td>52,372,706</td>
<td>FTO</td>
<td>25,344</td>
<td>41% (A)</td>
<td>+0.01 kg/m² per A allele in children</td>
<td>63</td>
</tr>
<tr>
<td>16.</td>
<td>rs5993409</td>
<td>16q22.2</td>
<td>52,372,706</td>
<td>FTO</td>
<td>38,759</td>
<td>40% (A)</td>
<td>+0.40 kg/m² per A allele</td>
<td>63</td>
</tr>
<tr>
<td>17.</td>
<td>rs5993409</td>
<td>16q22.2</td>
<td>52,372,706</td>
<td>FTO</td>
<td>32,387</td>
<td>41% (A)</td>
<td>+0.33 kg/m² per A allele</td>
<td>63</td>
</tr>
<tr>
<td>18.</td>
<td>rs1421065</td>
<td>4p13</td>
<td>25,345,455</td>
<td>FTO</td>
<td>2,790</td>
<td>40% (G)</td>
<td>+0.12 kg/m² per C allele</td>
<td>63</td>
</tr>
<tr>
<td>19.</td>
<td>rs1428333</td>
<td>16q22-q23</td>
<td>78,240,253</td>
<td>MAF</td>
<td>2,790</td>
<td>43% (A)</td>
<td>+0.09 kg/m² per A allele in children</td>
<td>63</td>
</tr>
<tr>
<td>20.</td>
<td>rs1805891</td>
<td>18q11.2</td>
<td>19,840,429</td>
<td>NPC1</td>
<td>2,790</td>
<td>44% (A)</td>
<td>+0.07 kg/m² per A allele in children</td>
<td>63</td>
</tr>
<tr>
<td>21.</td>
<td>rs1778131</td>
<td>16q16.3</td>
<td>54,012,977</td>
<td>MC4R</td>
<td>16,876</td>
<td>26% (C)</td>
<td>+0.22 kg/m² per C allele</td>
<td>64</td>
</tr>
<tr>
<td>22.</td>
<td>rs1778131</td>
<td>16q16.3</td>
<td>54,012,977</td>
<td>MC4R</td>
<td>32,387</td>
<td>22% (A)</td>
<td>+0.22 kg/m² per C allele</td>
<td>61</td>
</tr>
<tr>
<td>23.</td>
<td>rs1778131</td>
<td>16q16.3</td>
<td>54,012,977</td>
<td>MC4R</td>
<td>2,790</td>
<td>17.5% (C)</td>
<td>+0.09 kg/m² per C allele</td>
<td>63</td>
</tr>
<tr>
<td>24.</td>
<td>rs12970154</td>
<td>18p22</td>
<td>56,035,730</td>
<td></td>
<td>25,344</td>
<td>30% (A)</td>
<td>+0.36 kg/m² per A allele</td>
<td>65</td>
</tr>
<tr>
<td>25.</td>
<td>rs32830871 (12s31L)</td>
<td>18p11.2</td>
<td>56,189,806</td>
<td></td>
<td>16,797</td>
<td>0.73% (G)</td>
<td>+0.33 SD of their BMI Z-score</td>
<td>67</td>
</tr>
<tr>
<td>26.</td>
<td>rs2246461 (V1031)</td>
<td>18q13.1</td>
<td>65,909,565</td>
<td>CCHS8, KCTD15</td>
<td>7,713</td>
<td>2% (1031)</td>
<td>-0.48 kg/m² per 1031 allele</td>
<td>67</td>
</tr>
<tr>
<td>27.</td>
<td>rs23942</td>
<td>18q13.1</td>
<td>39,001,372</td>
<td>CHST8, KCTD15</td>
<td>25,344</td>
<td>70% (G)</td>
<td>+0.46 kg/m² per A allele in children</td>
<td>62</td>
</tr>
<tr>
<td>28.</td>
<td>rs1104753</td>
<td>18q13.1</td>
<td>39,001,372</td>
<td>CHST8, KCTD15</td>
<td>32,387</td>
<td>67% (G)</td>
<td>+0.06 kg/m² per G allele</td>
<td>61</td>
</tr>
</tbody>
</table>

**SNPs:**
- **NEGR1:** neuronal growth factor regulator 1
- **SECK1B:** secretoneurin 1B
- **BDNF:** brain-derived neurotrophic factor
- **TMEG1B:** thrombin and matrix metalloproteinase 17
- **SPS6:** sphingosine kinase
- **EPT51:** epithelial cell factor 51
- **DGK1:** diacylglycerol kinase
- **GNPDA:** glucosamine-6-phosphate deaminase
- **PRL:** prolactin
- **PTER:** phosphatidylethanolamine
- **MTCH2:** mitochondrial carrier homologue 2 (C. elegans)
- **BCIN1D1A:** BCIN1 domain containing 1A
- **SICT1:** synaptic activity regulator 1
- **MC4R:** melanocortin 4 receptor
- **CHST8:** carbohydrate (N-acetyl-galactosamine 4-6) sulfotransferase 8
- **KCTD15:** potassium channel tetramener domain containing 15

**Genes and Proteins:**
- **NEGR1:** neuronal growth factor regulator 1
- **SECK1B:** secretoneurin 1B
- **BDNF:** brain-derived neurotrophic factor
- **TMEG1B:** thrombin and matrix metalloproteinase 17
- **SPS6:** sphingosine kinase
- **EPT51:** epithelial cell factor 51
- **DGK1:** diacylglycerol kinase
- **GNPDA:** glucosamine-6-phosphate deaminase
- **PRL:** prolactin
- **PTER:** phosphatidylethanolamine
- **MTCH2:** mitochondrial carrier homologue 2 (C. elegans)
- **BCIN1D1A:** BCIN1 domain containing 1A
- **SICT1:** synaptic activity regulator 1
- **MC4R:** melanocortin 4 receptor
- **CHST8:** carbohydrate (N-acetyl-galactosamine 4-6) sulfotransferase 8
- **KCTD15:** potassium channel tetramener domain containing 15
**Summary of Genome-wide association studies (GWAS) or meta-analysis for obesity in humans**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Different GWAS study</th>
<th>Sample size in detected cohort</th>
<th>Predecessors of detected cohort</th>
<th>Parameter(s)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>WTCCC</td>
<td>1924</td>
<td>Europeans</td>
<td>BMI for quantitative analysis</td>
<td>64</td>
</tr>
<tr>
<td>2.</td>
<td>Sardinia</td>
<td>4741</td>
<td>Europeans</td>
<td>BMI for WC and quantitative analysis</td>
<td>75</td>
</tr>
<tr>
<td>3.</td>
<td>LOLIPOP</td>
<td>2684</td>
<td>Indian Asians</td>
<td>Analysis of IR and related quantitative phenotypes</td>
<td>79</td>
</tr>
<tr>
<td>4.</td>
<td>-</td>
<td>16,876</td>
<td>Northern Europeans</td>
<td>BMI for quantitative analysis</td>
<td>64</td>
</tr>
<tr>
<td>5.</td>
<td>The CHARGE consortium</td>
<td>31,373</td>
<td>Europeans</td>
<td>WC for quantitative analysis</td>
<td>83</td>
</tr>
<tr>
<td>6.</td>
<td>The GIANT consortium</td>
<td>38,580</td>
<td>Europeans</td>
<td>WC and WHR for quantitative analysis</td>
<td>12</td>
</tr>
<tr>
<td>7.</td>
<td>-</td>
<td>775 cases and 3197 unascertained controls</td>
<td>Europeans</td>
<td>Extreme obesity or BMI</td>
<td>84</td>
</tr>
<tr>
<td>8.</td>
<td>-</td>
<td>1380 and 1416 age-matched normal-weight controls</td>
<td>Europeans</td>
<td>Early onset and morbid adult obesity</td>
<td>63</td>
</tr>
<tr>
<td>9.</td>
<td>DeCODE</td>
<td>37,347</td>
<td>Europeans &amp; African Americans</td>
<td>BMI for quantitative analysis</td>
<td>62</td>
</tr>
<tr>
<td>10.</td>
<td>The GIANT consortium</td>
<td>32,387</td>
<td>Europeans</td>
<td>BMI for quantitative analysis</td>
<td>61</td>
</tr>
<tr>
<td>11.</td>
<td>-</td>
<td>487 extremely obese young cases and 442 healthy lean controls</td>
<td>Europeans</td>
<td>Extreme obesity or BMI</td>
<td>85</td>
</tr>
<tr>
<td>12.</td>
<td>-</td>
<td>453 extremely obese young cases and 435 healthy lean controls</td>
<td>Europeans</td>
<td>Extreme obesity or BMI</td>
<td>86</td>
</tr>
<tr>
<td>13.</td>
<td>KARE</td>
<td>8842</td>
<td>Asian</td>
<td>BMI, WHR for quantitative analysis</td>
<td>87</td>
</tr>
<tr>
<td>14.</td>
<td>MAGIC</td>
<td>77,167</td>
<td>Europeans</td>
<td>WHR for quantitative analysis</td>
<td>88</td>
</tr>
<tr>
<td>15.</td>
<td>-</td>
<td>123,865</td>
<td>Europeans</td>
<td>BMI for quantitative analysis</td>
<td>89</td>
</tr>
</tbody>
</table>

BMI: Basal metabolic index; WC, waist circumference; WHR, waist to hip ratio; IR, insulin resistance
Strategic approach towards analysis of obesity in humans

Approaches in the study of obesity

Candidate gene/SNP analysis

- Functional
- Positional

Genome-wide approaches

- GWLS
- GWAS

Epigenetic approach (Mitochondrial study)
Continuous NCD outcomes follow-up
مطالعه قند و لیپید تهران

Tehran lipid and Glucose Study

فاز اول
• 1380-1382
• پانزده هزار نفر شرکت کننده

فاز دوم
• 1383-1389
• تشکیل بانک زنومی

فاز سوم
• 1387-1390
• رسم 5400 شجره خانوادگی

فاز چهارم
• 1390-1393
• عقد تفاهمنامه چهت انجام مطالعه گسترده زنومی

فاز پنجم
• 1394-1397
• ارسال نمونه و انجام زنوتایپینگ

فاز ششم
• 1397-1399
• دریافت نتایج، کنترل کیفی نتایج و آزمون های آماری

همصد هزار مارکر
ژنتیکی

13894
خانواده

۳۹۵۹
نفر

13877
۲۵۰۰۰
شجره خانوادگی

13778
۱۳۰۰۰
نفر

2002-2005
14745
2006-2008
15693
2009-2011
15982
2012-2014
17186
1999-2001
11378

Tehran cardiometabolic genetic study

۵۰کریستال
۱۰۰کریستال
جمع آوری یک جمعیت
پزشک شامل بیمار و سالم در
یک مطالعه آینده نگر
بررسی کسرده زنومی با
انجام زنوتایپینگ
پایش و پیرايش داده ها
بررسی ارتباط زنوتیپ و
فنوتیپ

پیرايش افراد
پیرايش زنوتیپ ها

1. Meta-analysis
Cohort: SNP OR (95% CI)
Study A: 1.18 (1.06-1.32)
Study B: 1.12 (1.00-1.26)
Study C: 1.13 (1.02-1.25)
Replication: 1.21 (1.10-1.35)
Total: 1.19 (1.13-1.25)

2. Functional analysis
a. EMSA or b. reporter assay

3. Other analysis
Gene-based analysis, pathway analysis, polygenic risk estimation, SNP-SNP interaction, etc.
How a genome-wide association study works

Non Obese PEOPLE

Allele frequency

SNP: 1 2 3 4 5

AC GC TA AC GT

Obese PEOPLE

Allele frequency

SNP: 1 2 3 4 5

AC GC TA AC GT
Genome-Wide Association Study