Colloque “Rein et Obésité”
Académie de Médecine
Paris, 9 Mars 2016

Les gènes de l'obésité
Dr Amélie Bonnefon
The global epidemic of obesity

Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants

Lancet 2016; 387: 1377-96
Obesity is a genetic disorder.
Heterogeneity of the genetics of obesity

- **MONOGENIC FORMS**
  - Early-onset, severe obesity
  - Syndromic forms of obesity

- **POLYGENIC FORMS**
  - Most common form (>90% of cases)
  - Heritability: ~70%
Heterogeneity of the genetics of obesity

- **Monogenic forms**
  - Early-onset, severe obesity
  - Syndromic forms of obesity

- **Polygenic forms**
  - Most common form (>90% of cases)
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**Environment**
Legacy of genome-wide association studies (GWAS)

-> GWAS: Hypothesis of ‘Common Disease, Frequent Variants’

**CONTROLS** = normal weight subjects

**CASES** = obese subjects

**BMI, WHR, body fat**

Bimodality

Binary logistic regression

Linearity

Linear regression
Legacy of genome-wide association studies (GWAS)
Genetic studies of body mass index yield new insights for obesity biology
Expression of obesity-associated genes

- Whole brain
  - Substantia nigra
  - Hypothalamus
  - Pituitary gland
- Dorsal root ganglion
- Insula
- Caudate Nucleus
- Hippocampus
- Frontal lobe
- Heart
- Lung
- Liver
- Whole pancreas
  - Exocrine pancreas
  - Islet
  - FACS-sorted beta-cell
  - LCM beta-cell
  - EndoC-βH1
- Kidney
- Colon
- Small intestine
- Adipose tissue / pre-adipocyte / mature adipocyte
- Skeletal muscle
Expression of obesity-associated genes

Samples:
- Kidney
- Heart
- Small Intestine
- Colon
- Liver
- Dorsal Root Ganglion
- Adipose tissue
- Lung
- Islet
- FACS sorted Beta cell
- EndoC-BetaH1
- Exocrine pancreas
- LCM Beta cell
- Pre-adipocyte
- Mature adipocyte
- Skeletal muscle
- Frontal Lobe
- Caudate Nucleus
- Hypothalamus
- Pituitary gland
- Insula
- Brain
- Hippocampus
- Substantia Nigra

Plot showing expression levels with addiction, behavior, and reward markers.
Expression of obesity-associated genes

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-log_{10} Pvalue
Obesity-related GRS and diabetic kidney disease

“Obesity has been posited as an independent risk factor for both diabetic and nondiabetic renal disease. However, epidemiologic studies have produced conflicting results, and establishing causality from observational data is difficult.”

Genetic Evidence for a Causal Role of Obesity in Diabetic Kidney Disease

Diabetes 2015;64:4238–4246 | DOI: 10.2337/db15-0254
In 6,049 subjects with type 1 diabetes, they used a genetic risk score (GRS) including 32 validated BMI loci.
Heterogeneity of the genetics of obesity

GENE

- MONOGENIC FORMS
  - Early-onset, severe obesity
  - Syndromic forms of obesity

- POLYGENIC FORMS
  - Most common form (>90% of cases)
  - Heritability: ~70%

ENVIRONMENT
Genes involved in non-syndromic monogenic obesity

⇒ A central role of the Hypothalamus and of the Leptin-melanocortin pathway in the regulation of food intake
Genes involved in non-syndromic monogenic obesity

⇒ A central role of the Hypothalamus and of the Leptin-melanocortin pathway in the regulation of food intake

Monogenic obesity genes
Genes involved in monogenic obesity – *LEP*

=> Child with genetic deficiency of leptin can be “cured” by recombinant leptin.
Genes involved in monogenic obesity – *MC4R*

In Europe, the penetrance of *MC4R* mutations is generation- and age-dependent (Stutzmann et al. Diabetes 2008)

- 21st century children carrying *MC4R* mutations have 80% risk to be obese.
- Only 10% of their parents carriers were obese when young but currently 40% are obese.
Genes involved in monogenic obesity – *MC4R*

Genetic Variants in *LEP, LEPR, and MC4R* Explain 30% of Severe Obesity in Children from a Consanguineous Population

Sadia Saeed¹, Amelie Bonnefond², Jaida Manzoor³, Faiza Shabir³, Hina Ayesha⁴, Julien Phil Emmanuelle Durand², Hutokshi Crouch¹, Olivier Sorb², Muhammad Ali⁵, Taed Butt⁹, Ahs Mario Falchi⁷, Muhammad Arslan⁶,¹⁰, and Philippe Froguet¹,²,³,⁴

All obese children are from consanguinous families and are homozygous for these mutations.

Heterozygous *MC4R* carrier parents are NOT obese which shows the key role of the permissive environment in the mutation penetrance.
Genes involved in monogenic obesity – PCSK9

Wide spectrum of phenotypes related to PCSK1 variants

Effect size

Homozygosity of highly deleterious variants / malabsorptive diarrhea, failure to thrive during early infancy associated with high mortality rate, mild obesity...

Homozygosity (or compound heterozygosity) of less deleterious variants / severe early onset obesity, malabsorptive diarrhea and other features (reactive hypoglycemia)

Heterozygosity of highly deleterious variants / familial obesity (and glucose intolerance)

Partial loss-of-function heterozygous variants / increased risk of obesity

Coding SNPs / mild increase in risk of common obesity, and modest variations of both fasting proinsulin and fasting glucose

The number and the nature of the mutated alleles explain the severity of the obesity phenotype and associated clinical features
=> In 44 children with severe obesity and PWL, 198 children with severe obesity, 568 adults with morbid obesity and 383 controls

**OR=21; P=9.3×10^{-4}**
Genes involved in monogenic obesity – SIM1

T46R/ H323Y/ T714A  
OR=28  
P=5.6×10⁻³

Others  
P=0.158
Genes involved in monogenic obesity – *SIM1*

**T46R/H323Y/T714A**

- Adults with morbid obesity (*N*=9)
- Adults or children with severe obesity and PWL (*N*=4):
  - Developmental delay
  - Intellectual disability
  - Behavioural problems
  - Facial dysmorphism
  - No hypotonia no hypogonadism

**Overweight adult (*N*=1)**

**CONCLUSIONS:**

- Incomplete penetrance... environment (cf *MC4R*)? Epigenetics? Modifiers?
- All *SIM1* mutations are not functional... problems in the molecular diagnostic
# Alström Syndrome Typical Disease Progression

<table>
<thead>
<tr>
<th>Age</th>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Photophobia and Cardiomyopathy – Congestive Heart Failure</td>
</tr>
<tr>
<td></td>
<td>Progressive vision loss and blindness</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance / Hyperinsulinemia</td>
</tr>
<tr>
<td></td>
<td>Hearing loss</td>
</tr>
<tr>
<td></td>
<td>Liver Failure</td>
</tr>
<tr>
<td>10-15 yr</td>
<td>Type 2 Diabetes</td>
</tr>
<tr>
<td>20-40 yr</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Alström Syndrome is a progressive disease. As the child grows older, more medical complications become present. Most children are lost in their late teens and early twenties due to these medical complications.
Renal failure and monogenic (syndromic) obesity

Alström Syndrome: due to recessive mutations in *ALMS1*

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A Role for Alström Syndrome Protein, Alms1, in Kidney Ciliogenesis and Cellular Quiescence

Guochun Li¹, Raquel Vega¹, Keats Nelms², Nicholas Gekakis¹, Christopher Goodnow³,⁴, Peter McNamara⁵*, Hua Wu⁶, Nancy A. Hong⁵, Richard Glynne¹*
Renal failure and monogenic (syndromic) obesity

Bardet-Biedl syndrome

<table>
<thead>
<tr>
<th>PRIMARY FEATURES</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rod-cone dystrophy</td>
<td>93%</td>
</tr>
<tr>
<td>Post-axial polydactyly</td>
<td>69%</td>
</tr>
<tr>
<td>Truncal obesity</td>
<td>72%</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>98%</td>
</tr>
<tr>
<td>Renal anomalies</td>
<td>24% (only 52% of patients had undergone renal examination)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECONDARY FEATURES</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech disorder/delay</td>
<td>54%</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>50%</td>
</tr>
<tr>
<td>Behaviour</td>
<td>33%</td>
</tr>
<tr>
<td>Ataxia/imbalance</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6%</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>7%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>NA</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>21%</td>
</tr>
<tr>
<td>Facial features</td>
<td>NA</td>
</tr>
<tr>
<td>Hirschprung disease</td>
<td>NA</td>
</tr>
<tr>
<td>Situs inversus</td>
<td>NA</td>
</tr>
<tr>
<td>Polyuria/polydipsia</td>
<td>NA</td>
</tr>
<tr>
<td>Dental crowding</td>
<td>NA</td>
</tr>
<tr>
<td>Anosmia</td>
<td>60%</td>
</tr>
</tbody>
</table>
## Renal failure and monogenic (syndromic) obesity

### Bardet-Biedl syndrome

Table 2  BBS genes identified so far (*IFT* intraflagellar transport)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Method of discovery</th>
<th>Chromosomal location</th>
<th>Cellular localisation</th>
<th>Domains</th>
<th>Putative function</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBS1</td>
<td>Linkage analysis</td>
<td>11q13</td>
<td>Basal body/cilium</td>
<td>None</td>
<td>Cilia function</td>
</tr>
<tr>
<td>BBS2</td>
<td>Positional cloning</td>
<td>16q21</td>
<td>Basal body/cilium</td>
<td>None</td>
<td>Cilia function/flagellum formation</td>
</tr>
<tr>
<td>BBS3/ARL6</td>
<td>Linkage analysis</td>
<td>3p12-q13</td>
<td>Basal body/cilium</td>
<td>GTP-binding</td>
<td>Vesicle trafficking</td>
</tr>
<tr>
<td>BBS4</td>
<td>Positional cloning</td>
<td>15q23</td>
<td>Pericentriolar/basal body</td>
<td>TPR/PilF</td>
<td>Microtubule transport</td>
</tr>
<tr>
<td>BBS5</td>
<td>Comparative genomics</td>
<td>2q31</td>
<td>Basal body/cilium</td>
<td>DM16 DUF1448</td>
<td>Cilia function/flagellum formation</td>
</tr>
<tr>
<td>BBS6/MKKS</td>
<td>Mutation analysis</td>
<td>20p12</td>
<td>Basal body/cilium</td>
<td>TCP1 chaperonin</td>
<td>Cilia function/flagellum formation</td>
</tr>
<tr>
<td>BBS7</td>
<td>Similarity to BBS2</td>
<td>4q32</td>
<td>Basal body/cilium</td>
<td>TPR/PilF</td>
<td>IFT particle assembly</td>
</tr>
<tr>
<td>BBS8/TTC8</td>
<td>Similarity to BBS4</td>
<td>14q31</td>
<td>Basal body/cilium</td>
<td>TPR/PilF</td>
<td>IFT particle assembly</td>
</tr>
<tr>
<td>BBS9/B1</td>
<td>Homozygosity mapping with SNP arrays</td>
<td>7p14.3</td>
<td>Unknown</td>
<td>COG1361 membrane biogenesis</td>
<td>Unknown—expressed in bone cells</td>
</tr>
<tr>
<td>BBS10</td>
<td>SNP arrays</td>
<td>12q21.2</td>
<td>Unknown</td>
<td>TCP1 chaperonin</td>
<td>Unknown</td>
</tr>
<tr>
<td>BBS11/</td>
<td>SNP arrays</td>
<td>9q31-34.1</td>
<td>Unknown</td>
<td>RING WD40 NHL Barmotin B-Box</td>
<td>E3 ubiquitin ligase</td>
</tr>
<tr>
<td>TRIM32</td>
<td>SNP arrays</td>
<td>4q27</td>
<td>Unknown</td>
<td>Type II chaperonin</td>
<td></td>
</tr>
</tbody>
</table>
Renal failure and monogenic (syndromic) obesity

Putative pathomechanism for renal cystic hyperplasia in BBS
Obésité monogénique

FAIM

Obésité polygénique

SATISFACTION/ADDICTION

Hypothalamus
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