Flagship Program of Precision Medicine for AsiaPacific Biomedical Silicon Valley

October 1, 2019

Shih-Feng Tsai
Institute of Molecular and Genomic Medicine
Department of Research Planning and Development
National Health Research Institutes
Outline

Flagship Program: Organization and Progress

  Sequencing facility and development goals
  Example of WGS applications

G2020 – Sequencing 10K genomes for Taiwan patients

G2025 – Sequencing 500K genomes for Taiwan patients
Flagship Program of Precision Medicine for AsiaPacific Biomedical Silicon Valley

Three-Generation Birth Cohort
Molecular Diagnosis and Registry System for Rare Genetic Disorders
Medical centers
Technology Investment and Management
Industries

MoST

Genetic Information System for Digital Healthcare in Taiwan

MoHW

Universities

NHRI

Taiwan Genomic Industry Alliance

New Corps: Products and Services
Flagship Program of Precision Medicine: After 2 Years

Taiwan Genomics Industry Alliance
Taiwan Rare Disease Network
Collaboration Network with Medical Centers
International Partnership
NovaSeq 6000 Arrived NHRI, Taiwan on September 26, 2017

https://support.illumina.com/sequencing/sequencing_instruments/novaseq-6000.html
WGS: Driver of Precision Medicine
Lifetime Healthcare Management

2017
Rare disease
Cancer

2018
Not-so-rare disease

2019

2020
Preventive medicine
Number of Genome Were Sequenced for Flagship Project
(2017.12-2019.8)

**Rare/ Difficult Diseases (Blood)**

- DDID: 354
- SCA: 32
- Rett: 38
- HI: 226
- EP: 781
- DN: 781

**Cancers (FF tumor/Normal)**

- Others: 9
- BC: 78
- UTUC: 107
- LC: 644
- HCC: 1131
- CLL: 1131

**Total: 1912**
Taiwan Rare Disease Network

Next-Gen Sequencing
Bioinformatic Analysis
Interpretation
Clinical Management
Social Support

Sample Collection  DNA Extraction  Sequencing  Alignment  Variant Calling  Annotation  Gene Discovery & Interpretation  Clinical Reporting  Systems Integration
Taiwan Rare Disease Network

Analyzed 139 families and identified disease-causing mutations in 88 families
(Diagnosis rate is 63.3%)

<table>
<thead>
<tr>
<th>No</th>
<th>Case Recruitment</th>
<th>Family</th>
<th>Patient</th>
<th>Family member</th>
<th>Total cases</th>
<th>Analysis finished (family)</th>
<th>Project PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Immunodeficiency</td>
<td>4</td>
<td>5</td>
<td>12</td>
<td>17</td>
<td>4 (4/4)</td>
<td>李文益 傅令娴 韩舒萍</td>
</tr>
<tr>
<td>2</td>
<td>Epilepsy</td>
<td>74</td>
<td>85</td>
<td>107</td>
<td>192</td>
<td>10 (8/10)</td>
<td>刘祐岑 周宜卿</td>
</tr>
<tr>
<td>3</td>
<td>Spinocerebellar ataxia</td>
<td>13</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>13 (8/13)</td>
<td>宋秉文 范建宏</td>
</tr>
<tr>
<td>4</td>
<td>Hearing impairment</td>
<td>21</td>
<td>53</td>
<td>32</td>
<td>85</td>
<td>8 (3/8)</td>
<td>吴振吉 郑彦甫</td>
</tr>
<tr>
<td>5</td>
<td>Rett syndrome</td>
<td>24</td>
<td>24</td>
<td>48</td>
<td>72</td>
<td>24 (14/24)</td>
<td>洪碧莲</td>
</tr>
<tr>
<td>6</td>
<td>General undiagnosed disease</td>
<td>143</td>
<td>161</td>
<td>209</td>
<td>370</td>
<td>80 (51/80)</td>
<td>林炫沛 牛道明靖永皓等</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>279</td>
<td>353</td>
<td>408</td>
<td>761</td>
<td>139 (88/139)</td>
<td></td>
</tr>
</tbody>
</table>
Case Study # 1

A 18-years old girl had eye and ear problems, multiple organs defects, unique facial features, and somewhat, developmental delay.
### Candidate genes

- Abnormality of the midface – 382 genes
- Facial palsy – 147 genes
- Hearing loss – 230 genes
- Midface retraction -175 genes

#### Clinical Information

**C.C.\& Symptom**
- Cleft palate and ASD noted at birth, poor weight gain, Short stature
- Bil. hearing impairment under H/A fitting also left ear otalgia articulation problem

**Sign**
- L't peripheral type facial palsy, midface hypoplasia, surgically corrected L't CL/CP middle face deformity, velopharynx narrow

**Diagnosis**

<table>
<thead>
<tr>
<th>Name</th>
<th>(中文)</th>
<th>(英文)</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital anomaly</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Genetic Studies**

- 101/07/03 Cytogenetic study: 46,XX
- 90/06/18 Chromosome study (TMWCH): 46, XX
- 102/01/31 Array CGH, IBMS project (report on 102/7/05): no specific abnormality
## TRDN088 Nonsynonymous Substitution

<table>
<thead>
<tr>
<th>TRDN ID</th>
<th>Total variants (less &lt; 1%)</th>
<th>Candidate variants</th>
<th>Fit model</th>
<th>Pass SIFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRDN088-01</td>
<td>954</td>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Fit inheritance model and pass SIFT

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr</th>
<th>Position</th>
<th>Ref</th>
<th>Var</th>
<th>Genotype</th>
<th>CDS</th>
<th>Amino acid change</th>
<th>SIFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD7</td>
<td>8</td>
<td>61775155</td>
<td>G</td>
<td>T</td>
<td>G/T</td>
<td>c.1873G&gt;T</td>
<td>p.Glu625*</td>
<td>Deleterious</td>
</tr>
</tbody>
</table>

### OMIM

<table>
<thead>
<tr>
<th>Location</th>
<th>Phenotype</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>8q12.2</td>
<td>CHARGE syndrome</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Hypogonadotropic hypogonadism 5 with or without anosmia</td>
<td>AD</td>
</tr>
</tbody>
</table>
TRDN088 Facial Features

Nationwide Children's Hospital

TRDN088-01
## Transethnic Comparative Genomics Analysis

<table>
<thead>
<tr>
<th>Collaborators</th>
<th>UTUC</th>
<th>Lung cancer</th>
<th>HCC</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>International</td>
<td>Hirosaki University, Japan</td>
<td>Dana-Farber Cancer Institute, USA</td>
<td>Houston Methodist Research Institute, USA</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>KCGMH, TPVGH</td>
<td>TPVGH, TMUH</td>
<td>TPVGH, TMUH</td>
<td>TPVGH, TMUH</td>
</tr>
</tbody>
</table>
The unique feature of UTUC in Taiwan

<table>
<thead>
<tr>
<th></th>
<th>Western Country</th>
<th>Japan</th>
<th>Taiwan</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F ratio</td>
<td>$3 : 1$</td>
<td>$2 : 1$</td>
<td>$1 : 1.2$</td>
</tr>
<tr>
<td>Renal pelvis / ureter / bladder</td>
<td>$3 : 1 : 51$</td>
<td>$4 : 1 : 95$</td>
<td>$1.5 : 1 : 5.4$</td>
</tr>
<tr>
<td>Upper tract / all urothelial tumor</td>
<td>$5-10 %$</td>
<td>$5 %$</td>
<td>$31.4 %$</td>
</tr>
<tr>
<td>UTUC incidence ($10^5$)</td>
<td>$&lt; 1$</td>
<td>$&lt; 1$</td>
<td>$3-4$</td>
</tr>
</tbody>
</table>

- Higher prevalence
- Rapidly progressing incidence
- Non-smoker, female gender, and chronic kidney disease

Eur Urol 2004;46:147
General urology 2004;325
Cancer 1999;85:1342
Materials and Methods

Sample collection

VGHTPE
- 40 UTUC tumors
- 20 UBUC tumors

KCGMH
- 20 UTUC tumors

Hirosaki
- 20 UTUC tumors

Genome profiles
- Portrayed
- Next generation sequencing
- CoreExome SNP array
Clinical demographic data of 80 UTUC cases

<table>
<thead>
<tr>
<th></th>
<th>VGHTPE</th>
<th></th>
<th>KCCMH</th>
<th></th>
<th>Hirosaki</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Number</td>
<td>17</td>
<td>23</td>
<td>7</td>
<td>13</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Age (year)</td>
<td>71.6</td>
<td>66.8</td>
<td>73.1</td>
<td>73.8</td>
<td>69.6</td>
<td>71.5</td>
</tr>
<tr>
<td>Smoking</td>
<td>0%</td>
<td>14.3%</td>
<td>0%</td>
<td>0%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Stage &lt;= 1</td>
<td>8</td>
<td>8</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Stage &gt;= 2</td>
<td>9</td>
<td>14</td>
<td>5</td>
<td>6</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Pre-OP eGFR &gt;= 60</td>
<td>6</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Pre-OP eGFR &lt; 60</td>
<td>11</td>
<td>14</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>High grade</td>
<td>16</td>
<td>23</td>
<td>6</td>
<td>10</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Low grade</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Genomic profiles of UTUC

- 71 paired samples
  - VGHTPE – 39 WGS
  - KCGMH – 10 WGS and 6 WES
  - Japan – 8 WGS and 8 WES
- Mutational signatures
- Tumor mutation burden (Neo-antigen)
- Common mutations (genes)
Mutational signatures from UTUC Cases

WES capture regions
Principal components analysis

Aristolochic acid (AA) Repair failure

Principal components analysis graph with labeled axes PC1 and PC2.
Mutational signatures between Groups

- **Aristolochic acid** $(S22)$: $p < 10^{-4}$
- **Kidney failure** $(S27)$: $p < 10^{-3}$
- **Age** $(S1)$: $p < 10^{-3}$
- **Alkylating agents** $(S11)$: $p < 10^{-4}$
- **BRCA1/2** $(S3)$: $p < 10^{-4}$
- **Defective DNA MMR** $(S6)$: $p < 10^{-4}$
- **Defective DNA MMR** $(S20)$: $p < 0.01$
- **Liver cancer** $(S12)$: $p < 10^{-4}$
- **Liver cancer** $(S16)$: $p < 10^{-4}$
- **Others**

AA – 28 samples
Repair failure – 15 samples
Others – 28 samples
Tumor mutational burden

Non-parameter t test
AA vs Repair failure: p = 0.01
AA vs Others: p < 10^4
Repair failure vs Others: p = 0.0083
Public Health Implication

*Potential Environmental Risk Factors ??*

- **TMB high:** AA associated, TMB medium: DNA REPAIRE-FAILURE associated, TMB low: others
- **Early onset** in OTHERS group compared to AA and REPAIRE-FAILURE groups.
- Male : Female = 1: 1.17 (Female predominance in OTHERS group)
Clinical Implication

Treatment Suggestion for UTUC

AA group (TMB high):
Immunotherapy or
Targeted therapy (FGFR3 inhibitor)

REPAIRE-FAILURE group (TMB medium)
Immunotherapy and/or
Targeted therapy (FGFR3 or PARP inhibitor)

Others group (TMB low):
Chemotherapy
Acknowledgements

National Health Research Institutes

Research Center

Dr. Shih-Feng Tsai
Dr. Po-Huang Chiang
Weng
DNA Sequencing core lab

VYM Genome

Dr. Tze-Tze Liu
Hui-Ying

Kaohsiung Chang Gung Memorial Hospital

Dr. Hao-Lun Lo

Taipei Veterans General Hospital

Dr. Tzu-Chun Wei

Hirosaki University Hospital

Dr. Chikara Ohyama
G2025 – Sequencing half a million genomes of Taiwanese patients

亞太先驅基因醫學計畫：提供病人全基因體定序作為臨床診治的基準
Population Genomics Links Research with Clinical at Scale

Fully Reap the Benefits of Big Data in the Context of Clinical Care

Accelerating the translation of new insights into clinical practice

Improve individual patient care with cohort-level knowledge
Improve translational research by enriching cohort information

Identify variants
Perform molecular assay
Aggregate molecular data
Normalize cohort clinical & molecular data

Integrate clinical data
Generate clinical report
Improve population knowledge
Clinical Research

Clinical Care
Interpret variant clinical impact
Identify biomarkers
Enabling a Learning Health Ecosystem

Validate

你的基因 我的基因 大家的健康
Summary

• The Flagship Program has built the infrastructure of conducting high-throughput sequencing service for implementing precision medicine in Taiwan
• We have establishes a system to serve the needs of WGS for rare disease and cancer.
• TRDN is a network of medical professionals, research programs, and patient advocacy groups to offer DNA diagnosis of unknown or rare diseases
• Transethnic comparative genomic study is a powerful way to reveal environmental/genetic interaction in cancers
• G2020/G2025 is the next level up. Seeking for inputs of clinical cases, research ideas, and collaborations
Acknowledgements

**National Health Research Institutes**
- Dr. Yung-Feng Lin
- Dr. Po-Huang Chiang
- DNA Sequencing core lab

**VYM Genome Research Center**
- Dr. Tze-Tze Liu
- Hui-Ying Weng

**Kaohsiung Chang Gung Memorial Hospital**
- Dr. Hao-Lun Lo

**TRDN**
(Taiwan Rare Disease Network)

**Taipei Veterans General Hospital**
- Dr. Tzu-Chun Wei

**Hirosaki University Hospital**
- Dr. Chikara Ohyama