Clinical Exome Sequencing at Baylor Whole Genome Laboratory: Molecular Diagnosis and Disease Gene Discoveries

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Laboratory Director, Whole Genome Laboratory
BCM WGL Launches Clinical Exome Sequencing Oct 2011

• ~ 5200 samples received, ~4200 cases finalized
• 85% peds; 15% adult
• Mostly neurologic
• In addition: skeletal disorders, pulmonary artery hypertension, cardiovascular dz
• Variety of referral sources – academic medical centers, private hospitals

MONTHLY GERMLINE AND CANCER WES SAMPLES: ~230

N=4200 ~25% molecular Dx fits with clinical picture - Pts now given option to consent to research analysis for 75% no Mol. Dx. rendered
Clinical Exome Sequencing at WGL

• Discoveries made
  – Diagnostic rates
  – Rare genetic events identified
  – New disease genes

• Lessons learned
  – Key elements of clinical exome
WES-Workflow for Proband Exome

Extraction of Patient DNA
Exome sequencing
Data filtering and annotation
Variant interpretation
Sanger sequencing
Reporting

Trio exome sequencing is also available from our laboratory now
Molecular Diagnosis Rate: Overall and by Phenotypic Groups

Overall (n=2000)

Non-neurologic (n=244)

Neurologic plus (n=1147)

Neurologic only (n=526)

Specific Neurologic (n=83)

504/2000=25%

25% Diagnostic Rate Maintained for 3384 patients

Yang, et al., JAMA, 2014
Inheritance Manners among the 504 Positives in WES 2000

AR, 36%
X-LINKED, 13%
Mito, 0.2%
AD, 53%
de novo, 74%
unknown, 14%
inherited, 11%
de Novo (AD: 74%; XL: 62%)
Findings against Textbook Expectations: Cases with Two Molecular Diagnoses (23/504) ~ 5%

<table>
<thead>
<tr>
<th>Cases</th>
<th>AD</th>
<th>AD</th>
<th>AR</th>
<th>AR</th>
<th>X-linked</th>
<th>Two Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>ANKRD11</strong></td>
<td><strong>ARID1B</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>ASXL3</td>
<td>ENG</td>
<td></td>
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<tr>
<td>3</td>
<td>CHD2</td>
<td>PRRT2</td>
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<td>4</td>
<td>CREBBP</td>
<td>PRICKLE2</td>
<td></td>
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<tr>
<td>5</td>
<td><strong>DYRK1A</strong></td>
<td>KAT6B</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td><strong>SCN1A</strong></td>
<td>SMARCA2</td>
<td></td>
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<tr>
<td>7</td>
<td>GLI2</td>
<td>IRF6</td>
<td></td>
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<tr>
<td>8</td>
<td><strong>DES</strong></td>
<td><strong>CLCN1</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>KCNT1</td>
<td>TTN</td>
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<tr>
<td>10</td>
<td>KIF5C</td>
<td>NRXN1</td>
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<tr>
<td>11</td>
<td>KMT2A</td>
<td>TCIRG1</td>
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<tr>
<td>12</td>
<td><strong>NF1</strong></td>
<td>GALNT3</td>
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<tr>
<td>13</td>
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<td>14</td>
<td>SYNGAP1</td>
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<td>15</td>
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<td>16</td>
<td><strong>ARID1B</strong></td>
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<td><strong>GRIA3</strong></td>
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<tr>
<td>17</td>
<td>EFHC1</td>
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<td></td>
<td><strong>SMC1A</strong></td>
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<tr>
<td>18</td>
<td>FBN2</td>
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<td></td>
<td></td>
<td><strong>PQBP1</strong></td>
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<tr>
<td>19</td>
<td>TPM1</td>
<td></td>
<td></td>
<td></td>
<td><strong>DMD</strong></td>
<td></td>
</tr>
<tr>
<td>20</td>
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<td>23</td>
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</tr>
</tbody>
</table>

Additional notes:
- AD+AD (7) cases are highlighted in blue.
- AD+AR (8) cases are highlighted in yellow.
- AD+XL (4) cases are highlighted in green.
- AR+AR (3) cases are highlighted in purple.
- AR+XL (1) cases are highlighted in pink.
## Findings against Textbook Expectations: Uniparental Disomy Detected in 5/504 Positive Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>UPD Type</th>
<th>Isodisomy Type</th>
<th>Causal Genes/disease</th>
<th>Mat age/ Pat age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1/M</td>
<td>Mat UPD 2</td>
<td>Partial</td>
<td>SCN9A (epilepsy, insen. Pain)</td>
<td>36/41</td>
</tr>
<tr>
<td>2</td>
<td>9.6/M</td>
<td>Pat UPD 2</td>
<td>Complete</td>
<td>CHRNG (pterygium, lethal)</td>
<td>19/18</td>
</tr>
<tr>
<td>3</td>
<td>20/F</td>
<td>Pat UPD 9</td>
<td>Complete</td>
<td>SIGMAR1 (ALS 16, juvenile)</td>
<td>32/28</td>
</tr>
<tr>
<td>4</td>
<td>4/M</td>
<td>Mat UPD 22</td>
<td>Complete</td>
<td>PLA2G6 (neuraxonal dystrophy)</td>
<td>27/33</td>
</tr>
<tr>
<td>5</td>
<td>15/F</td>
<td>UPD 3</td>
<td>Complete</td>
<td>SLC25A38 (anemia, sideroblastic)</td>
<td>n.a./n.a.</td>
</tr>
</tbody>
</table>

* Parental samples not available
Medically actionable incidental findings (95/2000: ~5%)

- Unrelated to the phenotype but with immediate implications
- ACMG recommended genes (56): Cancer predisposition, Cardiomyopathy, Long QT
- Non-ACMG: G-6-PD, Fabry disease, mt mutation conferring risk for hearing loss
## Examples of New Gene Discoveries Leading to Updated Reporting

<table>
<thead>
<tr>
<th>Case</th>
<th>Date-Original Report</th>
<th>Date-Disease Gene Discovery</th>
<th>Date-Updated Report</th>
<th>Gene</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>Dec 2012</td>
<td>Sep 2013</td>
<td>Oct 2013</td>
<td>MAGEL2</td>
<td>Prader-Willi-like, intellectual disability, autism</td>
</tr>
<tr>
<td>4</td>
<td>Feb 2013</td>
<td>Sep 2013</td>
<td>Sep 2013</td>
<td>FBXL4</td>
<td>Mitochondrial Encephalopathy</td>
</tr>
<tr>
<td>5-6</td>
<td>Oct 2012</td>
<td>Dec 2012</td>
<td>Jul 2013</td>
<td>WDR45</td>
<td>Neurodegeneration with brain iron accumulation 5</td>
</tr>
<tr>
<td>7</td>
<td>Mar 2013</td>
<td>May 2013</td>
<td>Jul 2013</td>
<td>DEPDC5</td>
<td>Familial focal epilepsy with variable foci</td>
</tr>
<tr>
<td>8</td>
<td>April 2012</td>
<td>Jun 2012</td>
<td>Jul 2013</td>
<td>SERAC1</td>
<td>3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome</td>
</tr>
<tr>
<td>9</td>
<td>Dec 2013</td>
<td>May 2014</td>
<td>May 2014</td>
<td>ADHC1</td>
<td>Xia-Gibbs syndrome</td>
</tr>
<tr>
<td>10</td>
<td>Jan 2013</td>
<td>Oct 2014</td>
<td>Oct 2014</td>
<td>PURA</td>
<td>Neonatal hypotonia, seizures and encephalopathy (5q31.3 microdeletion syndrome)</td>
</tr>
</tbody>
</table>
Clinical Exome Sequencing on Proband

Oct 2011-Jun 2012
First 250 Samples
Oct. 2013

Jun 2012-Nov 2013
Additional 2000 Samples
JAMA 2014
Oct. 2014

Currently
~200 samples/month
WES Version 3

Clinical Whole-Exome Sequencing
for the Diagnosis of Mendelian Disorders

Yaping Yang, Ph.D., Donna M. Muzny, M.Sc., Jeffrey G. Reid, Ph.D.,
Matthew N. Bainbridge, Ph.D., Alecia Willis, Ph.D., Patricia A. Ward, M.S.,
Alicia Braxton, M.S., Joke Beuten, Ph.D., Fan Xia, Ph.D., Zhiyv Niu, Ph.D.,
Matthew Hardison, Ph.D., Richard Person, Ph.D., Mir Reza Bekheirnia, M.D.,
Magalie S. Leduc, Ph.D., Amelia Kirby, M.D., Peter Pham, M.Sc., Jennifer Scull, Ph.D.,
Min Wang, Ph.D., Yan Ding, M.D., Sharon E. Plon, M.D., Ph.D.,
James R. Lupski, M.D., Ph.D., Arthur L. Beaudet, M.D.,
Richard A. Gibbs, Ph.D., and Christine M. Eng, M.D.

Molecular Findings Among Patients Referred for Clinical Whole-Exome Sequencing

Yaping Yang, PhD; Donna M. Muzny, MS; Fan Xia, PhD; Zhiyv Niu, PhD; Richard Person, PhD; Yan Ding, MD; Patricia Ward, MS;
Alicia Braxton, MS; Min Wang, PhD; Christian Buhay, BS; Narayanan Veeraraghavan, PhD; Alicia Hawes, BS; Theodore Chiang, MS;
Magalie Leduc, PhD; Joke Beuten, PhD; Jing Zhang, PhD; Weimin He, PhD; Jennifer Scull, PhD; Alecia Willis, PhD; Megan Landsverk, PhD;
William J. Craigier, MD, PhD; Mir Reza Bekheirnia, MD; Asbjorg Stray-Pedersen, MD, PhD; Pengfei Liu, PhD; Shu Wen, PhD; Wendy Akcar, PhD;
Hong Cai, PhD; Magdalena Walkiewicz, PhD; Jeffrey Reid, PhD; Matthew Bainbridge, PhD; Ankita Patel, PhD; Eric Boensveld, PhD;
Arthur L. Beaudet, MD; James R. Lupski, MD, PhD; Sharon E. Plon, MD, PhD; Richard A. Gibbs, PhD; Christine M. Eng, MD
Clinical Exome Sequencing at WGL

• Discoveries made
  – Diagnostic rates
  – Rare genetic events identified
  – New disease genes

• Lessons learned
  – Key elements of clinical exome
Key Elements of Clinical Exome

• Optimization wet lab assays
  – Improve exome coverage and turn-around time (TAT)

• Variant interpretations and classifications
  – SNVs, CNVs and AOH analyses
  – Don’t stop at one diagnosis, the patient could have blended phenotypes resulting from two single gene defects
  – Incorporating clinical expertise in exome reporting

• Building and sharing knowledge database

• New disease gene discoveries
Wes Version 1: ‘WGL’ – VCRome2.1 is ‘just right’

- **Coding Exons from**: Vega, CCDS, RefSeq,
- **Predicted coding exons from**: Contrast and GenScan.
  - 197K targets, 42Mb genomic region; NimbleGen Rebalanced x2

**Observation:**
Some regions not covered….still need ‘polishing’!
What about comparison with clinical panels?
What about ‘Medical Exome’?
Exome “Spike-in” design content

Spike-in PKv1 (WES Version 2)
1977 Genes (0.220 Mbp)
GeneTests
21 Clinical Panels

Spike-in PKv2 (WES Version 3)
3643 Genes (2.5 Mbp)
PKv1 design
OMIM
Selected Cancer Genes
Solved Clinical Cases

VCRome 2.1
Exome
42 Mbp

By Donna Muzny et al.
Evaluation of ~100 Positive Samples Tested by WES Version 2

- Would the molecular diagnoses for the 100+ cases have been made definitively if the samples had been tested by WES Version 1?

1. Start with causal variants in the 100+ cases tested by **WES V2**
2. Identify genomic coordinates for the causal variants
3. Plot sequence coverage across target regions of **WES V1**
4. Flag regions where coverage < 20X
WES Version 1 Would Have Missed Molecular Diagnoses for Three Cases

• 1.7 yr old male
  • **SDHAF1** Mitochondrial complex II deficiency [MIM: 252011]
  • Homozygous pathogenic variant: **c.156C>A (p.Y52X)**, 1/1:50:1:51

• 19.3 yr old male
  • **DOK7** Familial limb-girdle myasthenia (LGM) [MIM: 254300]
    Fetal akinesia deformation sequence [MIM: 208150]
  • Compound heterozygous **c.1138dup (p.A380fs)**, 1/0:45:40:85, and
    c.1476_1485dup (p.G496fs),

• 13 year old female
  • **ADCY5**, Dyskinesia, familial, with facial myokymia [MIM 606703]
  • **c.1253G>A (p.418Q)**, 0/1:8:18:26, de novo
Whole Exome Sequencing
Total samples: 5,100; Avg: 96.6% at ≥20X Coverage

- Mitochondrial Genome + Exome: July 2013
- HiSeq2500 Rapid Runs: Aug 2013
- Library Automation: Feb 2014
- WES Kapa Libraries: Apr 2014
- WES version 2: Sep 2014
- WES version 3: Sep 2014
PKv2 (WES Version 3) Design Performance
Includes GeneTests and OMIM (n=3643)
11Gbp, VCRome 2.1 exome + PKv2 Spike-in Design

- >3200 Genes at 100%
- Polished 700-800 Genes to 100%
- ~1000 ClinVar sites recovered
- ~2000 HGMD sites recovered

By Donna Muzny et al.
Lightning Capture: Reduced turnaround time in the wet lab

Standard Exome: 20 days

<table>
<thead>
<tr>
<th>Library</th>
<th>Capture</th>
<th>Sequencing</th>
<th>Mercury Analysis</th>
<th>Annotation, filtering, prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days</td>
<td>4 days</td>
<td>12 days</td>
<td>24 hrs</td>
<td>15 min.</td>
</tr>
</tbody>
</table>

Optimized workflow
Kapa enzyme

Optimized Hybridizations

HiSeq 2500

4.5 hrs 8 hrs 27 hrs 24 hrs 15 min.

Lightning Exome: 64 hrs (<3 days)

Demonstrated using three sample dataset, 11Gbp
>98% target bases at 20x;
>94% target bases at 40x;

By Donna Muzny et al.
Key Elements of Clinical Exome

• Optimization wet lab assays
  – Improve exome coverage and turn-around time (TAT)

• **Variant interpretations and classifications**
  – Analyses of single nucleotide variants (SNVs), as well as copy number variants (CNVs) and absence of heterozygosity (AOH) regions
  – Thorough data analyses
    • Explore all possible inheritance manners
    • Don’t stop at one diagnosis, the patient could have blended phenotypes resulting from two single gene defects
  – Incorporating clinical expertise in exome reporting

• Building and sharing knowledge database
• New disease gene discoveries
Rare Genetic Events: SCID due to compound heterozygous *IL7R* Mutations (SNV+CNV) Detected by WES and CMA

The case is solved combining genomic analysis by BOTH WES and CMA

Sporadic case of SCID: CNV + SNV = Aut Recess SCID
Case example

• 5 year old male
• Father is 39 yrs old, mother is 27 yrs old

• Clinical Presentation:
  ▪ Global developmental delay (a history of hypotonia, rolled at 12 mo, sat at 12 mo, walked at 2 yr, first words at 2.5 yr, still receives ST)
  ▪ Overweight (at 4y 8 mo, weight 90-95th ile)
  ▪ Mild joint laxity
  ▪ Genital anomalies
  ▪ Mild facial dysmorphisms
  ▪ Behavioral problems (aggression)

• Tested negative for Prader-Willi Syndrome (PWS)
Absence of Heterozygosity (AOH) on chromosome 14

Concurrent Illumina HumanExome-12v1 (cSNP) array analysis revealed contiguous regions of copy neutral Absence of Heterozygosity (AOH) on chromosome 14 (approximate 39 Mb, 14q11.2-14q22)
Case 5

- Sanger sequencing revealed that a novel variant c.896C>A (p.S299Y) in the *RIPK3* (NM_006871, chr14:24806905, 14q12, non disease associated gene) is homozygous in this individual, heterozygous in the mother and negative in the father. These data support maternal uniparental disomy (UPD) on chromosome 14 in this individual.
UPD(14)mat Resembles PWS

<table>
<thead>
<tr>
<th></th>
<th>This Patient</th>
<th>UPD(14)mat (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR</td>
<td>-</td>
<td>12/13</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>20ile</td>
<td>18/21</td>
</tr>
<tr>
<td>Short statue</td>
<td>25-50ile</td>
<td>20/24</td>
</tr>
<tr>
<td>Obesity</td>
<td>90-95ile</td>
<td>10/15</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>+</td>
<td>18/21</td>
</tr>
<tr>
<td>Feeding difficulties</td>
<td>+</td>
<td>9/25</td>
</tr>
<tr>
<td>Joint laxity</td>
<td>+</td>
<td>7/11</td>
</tr>
<tr>
<td>Facial dysmorphisms</td>
<td>+</td>
<td>16/20</td>
</tr>
<tr>
<td>Motor delay</td>
<td>+</td>
<td>17/25</td>
</tr>
<tr>
<td>Mental delay</td>
<td>Language delay</td>
<td>8/24</td>
</tr>
<tr>
<td>Premature puberty</td>
<td>Too young</td>
<td>11/12</td>
</tr>
</tbody>
</table>

Key Elements of Clinical Exome

- Optimization wet lab assays
  - Improve exome coverage and turn-around time (TAT)
- **Variant interpretations and classifications**
  - SNVs, CNVs and AOH analyses
  - **Thorough data analyses**
    - Explore all possible inheritance manners
    - Don’t stop at one diagnosis, the patient could have blended phenotypes resulting from two single gene defects
- Incorporating clinical expertise in exome reporting
  - Building and sharing knowledge database
  - New disease gene discoveries
Mosaicism in a parent causing recurrent AD condition in the family

• Clinical Presentation:
  • Twin brother delayed speech, developmental regression, autism/autistic spectrum, intellectual disability, seizure disorder, short stature, microcephaly, dysmorphic features, and congenital heart disease.
  • WES was requested on the proband only
  • Samples from twin brother, unaffected sister and parents were available for Sanger studies

SHANK3 SH3 and multiple ankyrin repeat domains 3, c.3329_3332del (p.I1110fs), chr. 22q13.33.
Both parents are negative, the twin brother is also heterozygous, the unaffected sister is negative,
Associated disease: Phelan-McDermid syndrome [MIM:606232], AD
# Blended Phenotypes with Two Diagnoses

<table>
<thead>
<tr>
<th>Case</th>
<th>Disease I</th>
<th>Disease II</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ataxia-telangiectasia</td>
<td>Spastic paraplegia 50</td>
</tr>
<tr>
<td>2</td>
<td>Carpenter Syndrome</td>
<td>Neurofibromatosis, type 1</td>
</tr>
<tr>
<td>3</td>
<td>Nicolaides-Baraitser syndrome</td>
<td>Dravet syndrome</td>
</tr>
<tr>
<td>4</td>
<td>Contractural arachnodactyly, congenital</td>
<td>Renpenning syndrome</td>
</tr>
<tr>
<td>5</td>
<td>Epilepsy, progressive myoclonic 5</td>
<td>Rubinstein-Taybi syndrome</td>
</tr>
<tr>
<td>6</td>
<td>Leigh syndrome, X-linked</td>
<td>Bardet-Biedl syndrome 10</td>
</tr>
<tr>
<td>7</td>
<td>Mental retardation, autosomal dominant 12</td>
<td>Mental retardation, X-linked 94</td>
</tr>
<tr>
<td>8</td>
<td>Cardiomyopathy</td>
<td>Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>9</td>
<td>Malformations of cortical development and microcephaly</td>
<td>Pitt-Hopkins-like syndrome 2</td>
</tr>
<tr>
<td>10</td>
<td>Rothmund-Thomson syndrome</td>
<td>Xeroderma pigmentosum, group C</td>
</tr>
<tr>
<td>11</td>
<td>Epilepsy, juvenile absence, susceptibility to, 1</td>
<td>Cornelia de Lange syndrome 2</td>
</tr>
</tbody>
</table>
Key Elements of Clinical Exome

- Optimization wet lab assays
  - Improve exome coverage and turn-around time (TAT)
- **Variant interpretations and classifications**
  - SNVs, CNVs and AOH analyses
  - Explore all possible inheritance manners
  - Don’t stop at one diagnosis, the patient could have blended phenotypes resulting from two single gene defects
  - **Incorporating clinical expertise in exome reporting**
    - Weekly WGL meeting
    - Monthly WES sign-out meeting: accessible worldwide from the internet
- Building and sharing knowledge database
- New disease gene discoveries
Key Elements of Clinical Exome

- Optimization wet lab assays
  - Improve exome coverage and turn-around time (TAT)
- Variant interpretations and classifications
  - SNVs, CNVs and AOH analyses
  - Explore all possible inheritance manners
  - Don’t stop at one diagnosis, the patient could have blended phenotypes resulting from two single gene defects
  - Incorporating clinical expertise in exome reporting
- Building and sharing knowledge database
  - Data submission from WGL to ClinVar, etc.
- New disease gene discoveries
**New Gene Discoveries**

**REPORT**

De Novo Truncating Mutations in *AHDC1* in Individuals with Syndromic Expressive Language Delay, Hypotonia, and Sleep Apnea

Mutations in *PURA* Cause Profound Neonatal Hypotonia, Seizures, and Encephalopathy in 5q31.3 Microdeletion Syndrome

**RESEARCH**

De novo truncating mutations in *ASXL3* are associated with a novel clinical phenotype with similarities to Bohring-Opitz syndrome
New Disease Gene Discoveries

• Opportunity for unsolved exome negative cases to join research studies

Patients versus Research Subjects

- Privacy protected, - Strict rules - Generalized individual consent process - Straightforward

Fire-Wall

HIPAA Health Insurance Portability and Accountability Act

e tc

- Privacy protected, - Strict rules - Customized consent process - Complicated - Includes data release/sharing options

Physician guided Research protocol directed

- Clinical variant data sharing: technically easy
- Obeying the rules: NOT TRIVIAL

Clinical lab beginning to be preferred pathway for sample recruitment!!!!
Global Collaborations are Essential

2nd IRDiRC Conference - Shenzhen

7 – 9 NOVEMBER, 2014  FUTIAN SHERATON HOTEL, SHENZHEN, CHINA