TPMI Presents: Translational Genomics Research Update, Opportunities and Challenges

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Outline

- What is the translational genomics laboratory (TGL)
  - Goal and equipment
- Update on current projects
- Highlight future projects
- A great opportunity exists
- Challenges to overcome

Translational Genomics Lab

- TGL is a modern, high throughput, high capacity genomics facility that translates research findings for a number of human disorders including autoimmune diseases, hCRC, hBOC, cardiomyopathies, and a variety of other complex human diseases.

- The goal of translational genomics is to employ genetic discoveries to improve disease outcomes by developing smarter diagnostics and targeted therapeutics.

Equipment

NanoDrop

Cubit

Agilent TapeStation

ABI 7500

Sequenom MassArray 4

Luminex 100/200

ABI 3500XL Genetic Analyzer

Agilent Microarray

Ion Chef

Ion Torrent PGM

Ion Torrent Proton

Projects for 2016

- Stargardt disease recurrent mutation panel
- Hereditary hearing loss recurrent mutation panel
- *HLA-B*27* tagSNP screening assay
- Cardiomyopathy recurrent mutation panel
- Sanger sequencing for common CRC genes (*MLH1, MSH2, MSH6, PMS2* and *APC*)

In progress

- <u>Comprehensive CRC Project</u>
  - Hereditary CRC/BOC recurrent mutation panel
  - Hereditary cancer NGS panel (21 genes)
  - Exon deletion/duplication assay for all 21 cancer genes
  - MSI assay for CRC (5 markers)
- Genome-wide CNV microarray test for developmental delay
- Oncomine Focus Oncology NGS panel

To be completed by end of 2016

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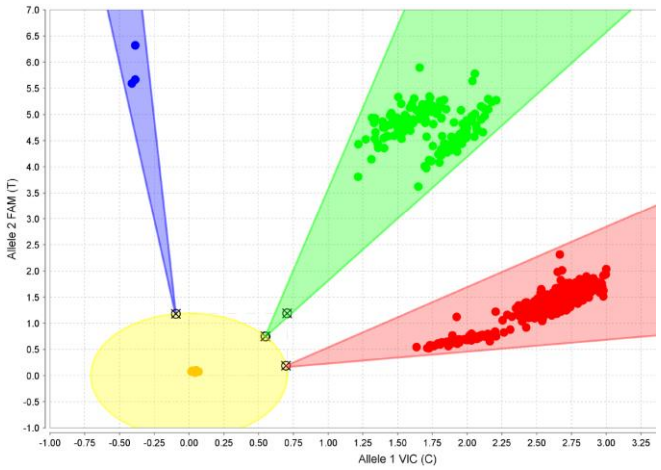
*HLA-B*27* tagSNP Screen Assay

- *HLA-B*27* is a first-line test for patients with ?axSpA.
- ~500 tests ordered annually in NL (positivity rate=17.0%).

- *HLA-B*27* tagSNP validation:
  - Analytical sensitivity=97.6%
  - Analytical specificity=99.9%
  - Analytical accuracy=99.6%
  - Analytical precision=100%



- The total sample cost of the current clinical test is $64.91, whereas the total sample cost the tagSNP assay is $3.28, which represents ~20-fold cost reduction (>$30,000/year).

- Expected policy change: ordering of the more expensive *HLA-B* locus test will be restricted to specialists with GPs permitted to only order tag-SNP screen assay.

Cardiomyopathy Mutation Panel

- A diagnostic panel of >20 mutations previously identified in the NL population known to cause cardiomyopathy has been designed.

Variant	rs number	Accession number	cDNA	gDNA
DSG2	rs121913006	NM_001943.3	c.146G>A, p.Arg49His	g.29099830G>A
DSG2	rs121913013	NM_001943.3	c.166G>A, p.Val56Met	g.29099850G>A
KCNJ2		NM_000891	c.1268G>A, p.Arg423Gln	g.68172448G>A
MYBPC3	rs199865688	NM_00256.3	c.2497G>A, p.Ala833Thr	g.47359047C>T
MYBPC3	Rs397516025	NM_00256.3	c.355G>A, p.Glu119Lys	g.47372104C>T
MYBPC3		NM_00256.3	c.2558delG, p.GLY853Alafs*26	g.47358986del
MYBPC3		NM_00256.3	c.710A>C, p.Tyr237Ser	g.47370037T>G
MYH7	rs3218716	NM_000257.2	c.2389G>A, p.Ala797Thr	g.23894525C>T
MYH7	rs193922390	NM_000257.2	c.5135G>A, p.Arg1712Gln	g.23884860C>T
MYH7	rs121913630	NM_000257.2	c.2167C>T, p.Arg723Cys	g.23895023G>A
MYH7		NM_000257.2	c.1757T>C, p.Val586Ala	g.23896925A>G
MYH7	rs45496496	NM_000257.2	c.2890G>C, p.Val964Leu	g.23893148
PKP2	rs193922674	NM_004572.3	c.2146-1G>C	g.32955491G>C
PKP2		NM_004572.3	c.1132C>T, p.Gln378X	g.33021899G>A
RYR2	rs190140598	NM001035.2	c.1258C>T, p.Arg420Trp	g.237608788
TTN		NM_001256850	c.66398G>A, p.Trp22133X	g.179439538C>T
TMEM43	rs113449357	NM_024334	c.934C>T, p.Arg312Trp	g.14180731C>T
TMEM43	rs63750743	NM_024334	c.1073C>T, p.Ser358Leu	g.21726C>T
TNNI3		NM_000363.4	c.485G>A, p.Arg162Gln	g.55665462C>T
TNNT2		NM_001001430.1	c.247G>A, p.Glu83Lys	g.201334755C>T

- Assay optimization and validation to be completed by September, 2016.

- Expected policy change: cardiomyopathy recurrent mutation panel will be utilized as a first-line test. Only those patients who test negative will reflex to gene sequencing panel.

Genetic Testing for Colorectal (CRC) & Breast/Ovarian Cancer (BOC)

- Recurrent mutation panel for CRC and BOC
- Sanger sequencing assay for CRC (*MLH1, MSH2, MSH6, PMS2* and *APC*) and BOC (*BRCA1 & BRCA2*)
- Multi-gene sequencing panel
- Exon deletion/duplication assay
- MSI assay for stage II CRC (5 markers)

- Expected policy change: recurrent mutation panel for CRC/BOC will be utilized as a first-line test for individuals at moderate- or high-risk of CRC/BOC. Only those patients who test negative will reflex to gene sequencing and multi-exon array panels. The mutation panel will replace targeted Sanger sequencing for families with known mutation.

- Estimated savings: $250,000/year

Projects – 2017 to 2018

- Cardiomyopathy targeted multi-gene NGS panel
- Hematological oncology multi-gene NGS panel
- Clinical whole-exome NGS panel

A great opportunity exists

- A single provincial medical genetics program (PMGP)

- A single medical genetics laboratory (MGL)
  - Shares footprint with the TGL
  - Vast array of genomic technologies in a single laboratory.

- Capitalize on IBM infrastructure through CHIA
  - Genetic variant database development; filtering and annotation pipeline; optimize testing algorithms.

- Funding exists through researchers at MUN & TPMI to investigate the genetics of specific diseases in the NL population & translate findings to the clinic.

Challenges to overcome

- Lack of available funding directed specifically towards translational genomics.
- Reach agreements between EH and MUN for equipment maintenance, replacement, test validation of genomic discoveries and human resource allocation.
- Genomic service provision agreement with MUN-MRP.
- Funding for lab technologist to perform genomic services.
- Infrastructure and operational funding for the BioBank.

Funding


MEMORIAL
UNIVERSITY
Faculty of Medicine


Eastern
Health


CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada


Atlantic Canada Opportunities Agency
Agence de promotion économique du Canada atlantique
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RDC
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