Clinical labs at a crossroads

Why we need a unified clinical-grade genomics database

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Our proposal to OGI...

To create Canada's unified, open-access, clinical- grade genetic database --using a commonly shared platform and designed to hold all types of information related to human gene variants and their relationship to rare and common diseases

Our major goal...

Moving collaboration to a whole new level for research + patient care

Lab directors - with clinicians, GCs, bioinformaticians, scientific community

To greatly expand quality, scale, scope
of our work

Very positive responses from community about our project...

Endorsements, collaborators, excellent feedback from “friendly” peer reviewers

Thanks to many in this room for letters of support

Status quo not an option...

Data scattered across institutions
Protocols, procedures vary widely
Weak phenotypic information
Errors, inconsistencies too common

Our successes - a mixed blessing

Next-gen technologies
Demand for whole-exome/genome
Mapping of non-coding DNA
Personalized medicine
Rising consumer expectations

Relentless pressure will continue for faster, more accurate analysis, interpretation, reporting

Not just a Canadian challenge...

Major US project led by Harvard's Heidi Rehm
Building on existing ClinVar database
Has won wide acceptance among US labs
Support for our project - inc. GeneInsight®
Adds strong resources to Cdn project

Supporting and participating labs

Three main aims...

Design variant assessment procedures
Extract and transfer data
Set up access and dissemination

The existing challenges...

Complexity of Novel Variant Assessment
Need for outside expertise
Eliminating misclassifications
State of translational research
Lack of physician training, experience
Regulatory approvals

Role of bioinformatics and IT...

Build system for variant interpretation
Define ontologies, structured phenotype data
Extract de-identified variant knowledge
Develop product to facilitate public access

Selected Elements of the NVA Procedure

Gene	MYBPC3
Exon	17
DNA	1504C>T
Protein	Arg502Trp

LOCUS SPECIFIC AND OTHER DATABASES

Disease Gene	dbSNP locus ID	GeneInsight	HGMD	GET-Evidence	PubMed	Google (IE) (non-IE)	UMD	Cardio Genomics	Interm Fil. DB	Leiden Muscular Dystrophy	Barth	Inherited Arrhythmias DB	ARVC DB	Cardio genomics SNPs	LMM Cardio Control Data	Mendelian Genes	TTR database	SCN5A LOVD	PTPN11-Base	RAS-MAPK Syndromes	LMM Noonan-CS-CFC DB	COSMIC	IARC TP53 DB	MUTp53GAD	LMM Germline p53 DB	MutDB	MMR DB	MMRLIV DB	InSIGHT Colon Cancer DB	Zhejiang Colon Cancer DB	TCA Cycle Gene Mut DB	ARUP MEN2 DB	Deafness Variant Database	LMM Usher DB	CCHMC-LOVD	Connexin-deafness	Ushbases	MitoMap	mtDB	Pendred-BOR DB	LMM Ohio Deafness DB	Comments
CARDIOMYOPATHY																																										
ABCC9	10060																																									
MYBPC3	4607																																									
PRKAG2	51422																																									
HEARING LOSS																																									
CDH23	64072																																									
SLC26A4	5172																																									
USH2A	7399																																									
NOONAN/MARFAN/CANCER																																									
KRAS	3845																																									
FBN1	3200																																									

Alamut.Common | Alamut.Orthologues | Variant | Control_Freq | **DB** | Publ+Internal_data | Internal_Families | Conserv_Biochem | Splicing | COSMIC(cancer_only) | Summary

Gene	MYBPC3
Exon	17
DNA	1504C>T
Protein	Arg502Trp
Link to current variant folder	
GeneInsight link	

Manual Internal Proband Chr		Segregation	0
Automated Internal Proband Chr	0/7870 (All)	Non-Segregation	0
		Double heterozygotes	0
Manual Lit Proband Chr		De novo variants	0
Automated Lit Proband Chr	N/A	Seen in different diseases?	

LMM data or Literature Reference	PMID	Family History?	PROBANDS # proband tested	# proband chrom tested	# positive HET probands	# positive HOM probands	positive proband phenotype(s)	Race matches case?	Allele frequency	# comp/double hets	# de novo variants	SEGREG # informative meioses	# non-segregations	CONTROL DATA # control chrom tested	# positive control chrom	Control race matches case?	Allele frequency	Functional Data	Comments (population details, familial testing, statistics, etc.)
American Indian or Alaska Native			17	34															
Ashkenazi Jewish			96	192															
Asian			220	440															
Black or African American			349	698															
Hispanic or Latino			124	248															
Mixed			99	198															
Native Hawaiian or Other Pacific Islander			8	16															
None			58	116															
Unspecified			601	1202															
White and Caucasian			2363	4726															
Internal race matched			0	0	0	0				0	0	0	0	0	0				
Internal all races			3935	7870	0	0				0	0	0	0	0	0				
Author, Year																			
Author, Year																			
Author, Year																			
Author, Year																			
Author, Year																			
Author, Year																			
Author, Year																			
Lit. race matched			0	0	0	0				0	0	0	0	0	0				
Literature all races			0	0	0	0				0	0	0	0	0	0				

Alamut.Common | Alamut.Orthologues | Variant | Control_Freq | DB | **Publ+Internal_data** | Internal_Families | Conserv_Biochem | Splicing | COS

What is GeneInsight?

GeneInsight® I Lab
for better care

Users GeneInsight Admin

Admin, M.L. | Log Out
User Guide | Support | Change Password

Variant List | p.Ser41delinsAs... | p.Leu8TrpfsX1...

Variant... Report...

Variant Details: XG1 *12 [c.21delG (p.Leu8TrpfsX13)] <<

Gene: XG1 (XD1,XD2)
Transcript: NM_020469.2 [7 Exons, Coding 1..7]
Allele: *12
Variant: *12 [c.21delG (p.Leu8TrpfsX13)]
Gene Region: Exon 1
Interp. Summary: Pathogenic Mild (XD1)
Resistant (XD2)
Interp. Status: Content Approved by M.L. Admin on 09/11/2012 07:31 PM.
Revision Approved by M.L. Admin on 09/11/2012 07:31 PM.

Edit Variant

Full Details | Frequency | Notes | References | Interpretation | Interp. History | Assessments | Seq. Alignments

Current Interpretation Edit | Request Re-approval | Re-approve | <<

Status
Content Approved by M.L. Admin on 09/11/2012 07:31 PM.
Revision Approved by M.L. Admin on 09/11/2012 07:31 PM.

Reason(s) For Update
New Evidence

Interpretations

Category/Inher./Excl.	Diseases/Drugs
Pathogenic Mild (RECESSIVE)	X1 Disease

Variant Interpretation

The Leu8fs variant (also referred to as the *12 allele) has been identified with a second pathogenic variant in >20 individuals with late-onset X1 Disease (Example et al 2008, Another et al 2010). This variant is also present in 1/8600 European American chromosomes from the NHLBI Exome Variant Server database. In summary, this variant is highly likely to be disease-causing.

Category/Inher./Excl.	Diseases/Drugs
Resistant	X2 Drug

Variant Interpretation

The Leu8fs variant (also referred to as the *12 allele) has been shown to be resistant to the X2 drug in a large cohort study of individuals with X1 Disease (Data et al 2011). Individuals who were homozygous for the Leu8fs variant did not show a reduction in symptoms over a three year period

A Canadian GeneInsight instance, we will give you a login!

No limit to number of users
Ensure users do not use the data beyond its intended use
Ability to share data within other labs using the system, including those in the United States
Each lab will need to make their own decision on whether they are comfortable sharing data with the Canadian installation
Incent labs to share, in a share and share alike fashion
Pull ClinVar data into GeneInsight so it becomes accessible through the system
We will also support pushing data into ClinVar for labs who are open to releasing data to the public

Thank you!

Please complete out short survey