The global initiative to
collect and curate all
human genetic variation
affecting human health

The Human Variome Project – Pilot project and progress

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THE HUMAN VARIOME PROJECT

What is the Human Variome Project?

(www.humanvariomeproject.org)

- Variome – Variation in a genome
- Human Variome Project – Collection & Distribution of Human Variation & its phenotype
- Initiated 20-23 June 2006 in Melbourne, Australia co-sponsored by WHO
- A community activity to collect for databasing
- Third HVP meeting at UNESCO Headquarters, Paris, May 2010

References

Nat Genet, 2007. **39**(4): p. 433-6.

Science, 2008. **322**(5903): p. 861-2.

What is happening in Variation

Genomics

- SNP, HapMap, and GWAS consortia providing variants and associations for NCBI/EBI

Genetics

- 1000 Genomes, Cancer Genomes
- Diagnostic labs/Clinicians gathering data for patient care
 - Locus Specific Databases (LSDB)
- Little incentive for public sharing of latter data
- Diagnostic lab/Clinicians spend hours/days/weeks searching the web
- No agreed integrated procedure

Why is complete data needed?

- Genetic clinicians and diagnostic lab heads consult mutation databases daily (and for hours per patient)
- Data needed to refine pathogenicity predictions
- Cohorts needed for mutation specific therapeutics trials
- Individuals with fully sequenced DNA need lists of mutations to inform themselves of risk
- Pre-marital counselling can be extended genome wide from Thalassaemia when we all have our genomes sequenced

Ultimate need

- A public catalogue of curated variation in each of 20,000 genes & associated phenotypes/studies
- An automated system of submission and review
- Improved genetic healthcare and research outcomes
- Costs and tasks will be shared worldwide

What is needed for inherited diseases?

- Worldwide agreed standardised systems, methods and standards to make submission/collection and sharing an easy and rewarding process
- A system which allows rapid access to all mutations by clinicians and laboratories to provide the best possible genetic healthcare (diagnosis, prognosis and therapy) and research
- A system for Locus Specific Databases (LSDBs) (gene-specific databases) for each gene/disease which are up to date and properly curated to eliminate errors.

What is the HVP trying to do?

Aims to:

- Improve health by unification of data
- Support collection and use data
- Gather experts and expertise to inform the task
- Worldwide inclusive project
- Planning Meeting held May 2008
- Roadmap approved April 2010
- Implementation Meeting – Paris, May 10-14, 2010 with the support of UNESCO
- Incorporation HVP International Sept 2010

Who will use the data?

- Clinicians
- Diagnostic lab heads
- Companies for cheap diagnostic strategies
- Researchers in therapy
- Personalised medicine companies
- Those with personal genomes

Factors mitigating against mutation capture

- No time available for submission
- Mutations and clinical detail documented by different individuals
- Ethical considerations
- New paradigm needed
- New software needed
- Accepted portal needed to relevant database
- Accepted database needed

A proposed pathway

HVP Working Groups

- Ethics
- Education
- Data Collection from Clinics
- Data Collection from Laboratories
- Data Transfer, Databasing & Curation (Gene Specific/LSDB)
- Overall Data Integration and Access
- Assessment of Pathogenicity
- Publication, Credit & Incentives
- Country Specific Collection
- Funding Mechanisms and Sustainability
- Nomenclature and Standards
- Translation to Healthcare

Projects which have progressed well

1. Nomenclature
2. Database content
3. Software
4. Central DB connectivity
5. Ethics
6. Disease pilots InSiGHT/Colon Cancer
7. Country pilots

HVP Working Group - Ethics

Co-Chairs: Sue Povey (UK)
Carol Barash (US),

Aim: Practical protocols (SOP) for LSDB curators

- Past ethics guidelines by lawyers and other non-curator persons
- Recently by Cotton et al *Hum Mutat* 26(5):489 (2005) for LSDBs
- Currently S. Povey clinician and curator (TSC1+2) to generate protocol by and for curators (in press)

HVP Working Group - Education

Co-chairs: Linda Roberts (US),
Elizabeth Shephard (UK)

- Education survey initiated to see where Working Group is headed
- HVP Session ASHG meeting Nov 1, 2010

HVP Working Group – Data Collection from Clinics

Co-chairs: Peter Byers (US),
David Rimoïn (US)

Discussion Leaders: Garry Cutting (US),
Gabriela Möölein (Germany)

- Software in development
- Form publication:- Hum Mutat, 2007. **28**(10): p. 931-2.

HVP Working Group – Data Collection from Laboratories

Chair: Graham Taylor (UK)

Discussion Leader: Sue Richards (US)

- Form publication:- Hum Mutat, 2007. **28**(10): p. 931-2.
- Software in development
- DMuDB system (UK)

HVP Working Group – Data Transfer, Databasing & Curation (Gene Specific/LSDB)

Chair: Johan den Dunnen (Netherlands)

Discussion Leader: Arleen Auerbach (US)

- LOVD
 - Developed by J. den Dunnen/HGVS (www.lovd.nl)
 - Open access and free to download
- UMD
 - Developed by C. Beroud (www.umd.necker.fr/)
- LSDB to central DB agreement
- LSDB content publications
- Reference sequence

HVP Working Group – Overall Data Integration and Access

Discussion Leaders: Anthony Brookes (UK),
Donna Maglott (US)

- GEN2PHEN group
- NCBI initiatives
- NCBI, UCSC and EBI support letters
- UCSC Genome Browser and NCBI have mounted LSDBs

HVP Working Group – Assessment of Pathogenicity

Discussion Leaders: Marc Greenblatt (US),
Sean Tavtigian (US)

Aim: To derive general method to assign pathogenicity or
not to variants – unclassified variants (UV)

- S. Tavtigian – Major IARC meeting Feb 2008
- 8 papers published in *Human Mutation* (2008) from meeting and are open access
- BRCA collaborators currently have meetings to decide pathogenicity
- InSiGHT has key committee
- Ideally algorithm to give category for chance of pathogenicity

HVP Working Group – Publication, Credit & Incentives

Chair: Myles Axton (US)

Discussion Leader: John Burn (UK)

Aim: To encourage and reward submission

- Microattribution campaign – M. Axton (Editorial, *Nat Genet* Aug 2007)
- Collect mutations from around world in gene and publish in one update – *Nat Genet* & *Hum Mutat*
- WayStation project – C. Talbot Jr.
(www.centralmutations.org)

HVP Working Group – Country Specific Collection

Co-Chairs: Raj Ramesar (Sth Africa),
Jumana Al-Aama (Saudi Arabia)

Discussion Leader: Joji Utsonomiya (Japan)

Aim: To collect all instances of mutations from all labs in a country

- Pilot 6-8 countries – Australia, Japan, UK, Korea, Spain
- Submit to LSDB/NCBI
- Establish/Procedure applicable to all genes
- Human Genetic Societies
- MutDB model (UK) – G. Taylor
- FINDbase/Ethnic databases model – G. Patrinos
- InSiGHT to model for four genes – F. Macrae
- Funding for Australian Node of the HVP

HVP Working Group – Funding Mechanisms & Sustainability

Chair: Michael Katz (US)

Discussion Leaders: Richard Cotton (Australia),
Daniela Seminara (US)

- Heighten credentials – WHO, UNESCO
- Adopt a Gene
- Funding in countries - Spain

HVP Working Group – Nomenclature and Standards

- Chair: Johan T den Dunnen
- Nomenclature developed by HGVS (www.hgvs.org) over many years
- To be spread to other genetic journals
- Relevant guidelines, etc document being developed from HGVS and other sources

Key Pilot and Affiliated Projects of HVP

- Australian Node of the HVP
- InSiGHT colon cancer database
- Nutrigenomics
- Neurogenetics Consortium

HVP Australian Node I

Why country specific collection

- Ensuring coherent genetic healthcare for family branches in different states
- Documentation of disease found
- Development of accurate and needed care strategies
- Development of relevant and economical diagnostic strategies for the dominant ethnic group and their diaspora around the world
- Spread the load of mutation collection
- Ensure world-wide complete collection
- Increase accuracy of pathogenicity prediction

HVP Australian Node II

- Consortium of Australian clinicians, diagnosticians and researchers
- Funding from the NeAT scheme for software and systems development to
 - Collect gene variation data from diagnostic laboratories
 - Linkage to clinical information
- Integration of other systems
 - BioGrid
 - Mawson
 - CGen

HVP Australian Node III

The Human Variome Project Australian Node will enable:

- Faster access to information
- Enhanced diagnosis
- Platform for research
- Integration with international data via gene/disease specific databases

This system will also serve as a model for collection in other countries

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The Human Variome Project – Summary of Country Specific Activity

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Letters of support for HVP received from individuals in following countries:

- Argentina
- Australia
- Austria
- Belgium
- Canada
- France
- Germany
- India
- Japan
- Mexico
- The Netherlands
- South Africa
- Sweden
- Switzerland
- Tunisia
- United Arab Emirates
- UK
- USA
- Zimbabwe

Have already established a national database (not HVP Node)	Started putting systems in place for collecting data for HVP Node	Applying for/Received Funding* (for HVP related Project)
<p>Cyprus Greece Israel Finland Singapore United Kingdom</p>	<p>Australia China Egypt India Korea Malaysia Spain</p>	<p>Australia* - (June, 2009) received federal funding to develop HVP Australian node.</p> <p>China – applying for funding for planning and implementation of HVP Chinese node</p> <p>Korea* - (Nov 2008) received government funding of \$80,000 USD for establishing a virtual Asia/Pacific Bioinformation Centre (ABC) and a variome project for Asia (AVP).</p> <p>Spain* - (Oct 2009) received funding from Galician government to establish neurogenetics database</p>

Forming/Formed* HVP Consortium	Interested in formally participating in HVP	
Australia* China* Egypt* Malaysia* Russia Spain	Argentina Australia Belgium China Croatia Egypt Finland Germany Greece Iceland India	Israel Japan Korea Kuwait Malaysia Russia Saudi Arabia Spain Thailand UAE

InSiGHT and

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the Human Variome Project Pilot Study Aims

- To pilot systems to register all variants in genes predisposing to GI cancer commencing with the MMR genes (hMLH1, hMSH2, hMSH6, PMS2)
- Other genes: APC, MUYTH, E Cadherin
- To be scalable to (all) other genes across the genome
- To develop country specific data nodes which
 - Integrate with other systems i.e.: HVP LSDBs, and then NCBI, EBI,
 - Has ease of access
 - Adaptable to all countries

Finlay A. Macrae

Progress of the InSiGHT/HVP collaboration

- Governance of the InSiGHT MMR gene database established, terms of reference agreed.
- Three related databases have merged and interacted through the InSiGHT database: The InSiGHT, Newfoundland, and the Dutch MMR missense database 500-10,000 & 20,000 hits/month
- Curation of database (M Woods, A Dowty, Jan 09)
- **LOVD** (Leiden Open Variant Database) selected

www.insight-group.org

www.med.mun.ca/MMRvariants/

www.mmruv.info

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Current Plans

- Incorporation of InSiGHT and registration as a charity (Jan 2010)
- MTA and MOU with UK DMuDB to upload all UK diagnostic lab variants
- Testing of phenotype data extraction at clinic level (Australia, Denmark, Sweden, Germany, Israel, others welcome)
- Assignment of pathogenicity derived from IARC/InSiGHT Bayesian analysis (S Tavtigian; M Greenblatt; S Lipkin)
- Mature operations of the Interpretation Committee (Paris, 2010)
- Software development for integration of disparate strands of data (Australian BioGrid, grant application to NCI (M Greenblatt, March 2009)
- National node connectivity development (NeAT grant, Australia, 2009-12)
- Communication strategies with NCBI and EBI (D Maglott, P Flicek: to do)
- Upload more national MMR data to the InSiGHT database
- Fund raising to support curation, and governance and, interpretation committees (“Adopt-a-gene”; New York fun run)
- Curator appointed Sept 2010

Finlay A. Macrae

General Handling of Functional Variations

- Define genotype and its effects
- Establish flows
- Establish databasing and access
- Establish curation
- Recent areas:
 - Inherited disease
 - Pharmacogenomics
 - Nutrigenomics
 - Not “SNPs”/ Association Studies

Databasing/Display Example I - Cancer

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COSMIC – Display of somatic mutations in tumours
www.sanger.ac.uk/genetics/CGP/cosmic/

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Databasing/Display Example II – VariVis

Timothy D Smith and Richard GH Cotton,
“VariVis: a visualisation toolkit for variation
databases.”

BMC Bioinformatics 2008, **9**:206

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Nutrigenomics Variation

- Variation in transport and metabolism of metals and vitamins
- Leads to variation in health outcomes
- Phenotype: - physical signs - pernicious anaemia
 - in vitro transport / metabolism
 - protein change
- Genotype: - base change in gene - HGVS Nomenclature

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The Micronutrient Genomics Project Operational Pipeline

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Recent Meetings' Publications

1. Satellite UNESCO HVP Meeting, Paris, May 2010
Kaput et al – in press
2. Publications – in preparation
3. NuGO Website: www.nugo.org

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HVP Neurogenetics Consortium

- Precipitated by a HVP article in Science (2008. **322**(5903): p. 861-2) featuring Neurogenetics
- Initiated at GDRC/HVP Forum in Honolulu 19 October 2009 – 80 attendees
- Funding from local Spanish Government for Dr. M-J. Sobrido
- Steering Committee of 8 leading neuro-geneticists from Spain, Germany, USA, UK, Egypt and Belgium
- Satellite meeting 10 May 2010 at HVP meeting at UNESCO
- Spastic Paraplegia database meeting Sept 2010

Some challenges for neurogenetic LSDBs ...

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- **Current database situation in neurogenetics insufficient / inefficient:**
 - Different structure and nomenclature, difficult interoperativity
 - Many genes/disorders not covered: **spastic paraparesis, dystonias...**
 - Genes/disorders duplicated, information difficult to compare or misleading
 - Insufficient multidisciplinary knowledge in curating teams
- **Need standards:**
 - Phenotype (TRAITS vs syndromes, subclinical information)
 - Assessment of pathogenicity
 - Needs combination of methods (bioinformatics, functional...)
 - Needs expert, disease-centered standards
 - Specific mutation types (mitochondrial, repeat expansions)
 - To capture evidence from association studies
 - Database structure and data submission
 - Ethics
- **Need strategies:**
 - To ensure collection of genetic data
 - To ensure collection of clinical data

} Identify factors that hamper data capture

... could be overcome by coordination.

Some suggestions / directions towards solutions

- **Develop a neuro-phenotype ontology with descriptors at the level of signs/symptoms in addition to syndromes**
- **A good start could be integration of data in existing databases**
- **“Quality stamp” for phenotype data: introduced once vs follow-up available**
- **Develop databases and informatic tools that support future upgrading of information content but are not continuously changing**
- **Agree upon a consensus database tool/structure**
- **Work together with big research groups producing high-throughput data to capture funding from key agencies**
- **Look for a model health institution with informatic records to go back to**

Strategies to ensure collection

- Journals demand data submission as a condition for publication
- Novel publishing strategies to ensure reward for publishing
 - super reviews
 - electronic publication
 - microattribution
- Mutation submission a condition of grants involving mutation discovery
- Mutation submission a condition of laboratory licensing
- Mutation submission a condition of quality assessment of laboratories
- Mutation submission part of local reporting regime
- Education of relevant clinicians and scientists
- Country & State specific collection
- Statutory requirement of submission to registers as per cancer cases
- Manuscript published:- Genet Med, 2009. **11**(12): p. 843-9.

Do you have data to submit?

- Inherited colon cancer especially
- Neurological disease especially spastic paraplegia
- **Do you wish to join:**
 - HVP Country or disease councils
 - HVP Consortium – single person
- Please contact:
R. Cotton – cotton@unimelb.edu.au via
www.humanvariomeproject.org

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3rd HVP Meeting

Implementation and Integration Meeting,
UNESCO Headquarters, Paris.
10-14 May 2010.

- Scientific Advisory Committee elected
- Roadmap approved
- Manuscript submitted

<http://www.humanvariomeproject.org/meetings/paris/>

Attendees at the 1995 meeting

R. Cotton

C. Sriver

V. McKusick

K. Fasman

J. Ostell

C. Fields

L-C Tsui

F. Hutchinson

M. Greenblatt

H. Kazazian

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HVP Initiating Meeting June 2006, Melbourne, Australia

HVP Planning Meeting, May 2008, San Feliu de Guixols, Spain

HVP doesn't believe its just all work!

3rd HVP meeting, Paris – Gala Dinner

Supporters

- CASS Foundation
- Buckland Foundation
- Federal Government of Australia
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- March of Dimes
- Myer Foundation
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