Unique Utah Resources For Cancer Gene Identification

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Cancer Gene Identification in Utah

The Utah Population Data Base (UPDB)
 Utah Genealogy
 Utah Cancer Registry (UCR)

Cancer Gene Identification using UPDB

- Cancer Gene Understanding using UPDB
- What Next?

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Utah Population Data Base History

- 1970's Mark Skolnick (University of Utah Department of Medical Informatics) proposed building a Utah population data base with genealogy linked to disease data
- Utah had genealogical data and population-wide cancer data
- The Iceland genealogy resource was already being developed, with plans to link limited medical records (deCode Genetics)

Utah Population Data Base Genealogy

- Members of the Church of Jesus Christ of Latter Day Saints (Mormons) make up 75% of the state of Utah
- 3-generation family genealogies submitted to the Family History Library by members of the Church
- Genealogies containing at least 1 life event in Utah or on the pioneer trail (1840-1850) were input and linked
- Original UPDB genealogy contained ~ 1.6 million individuals linked in genealogies 6 7 generations deep

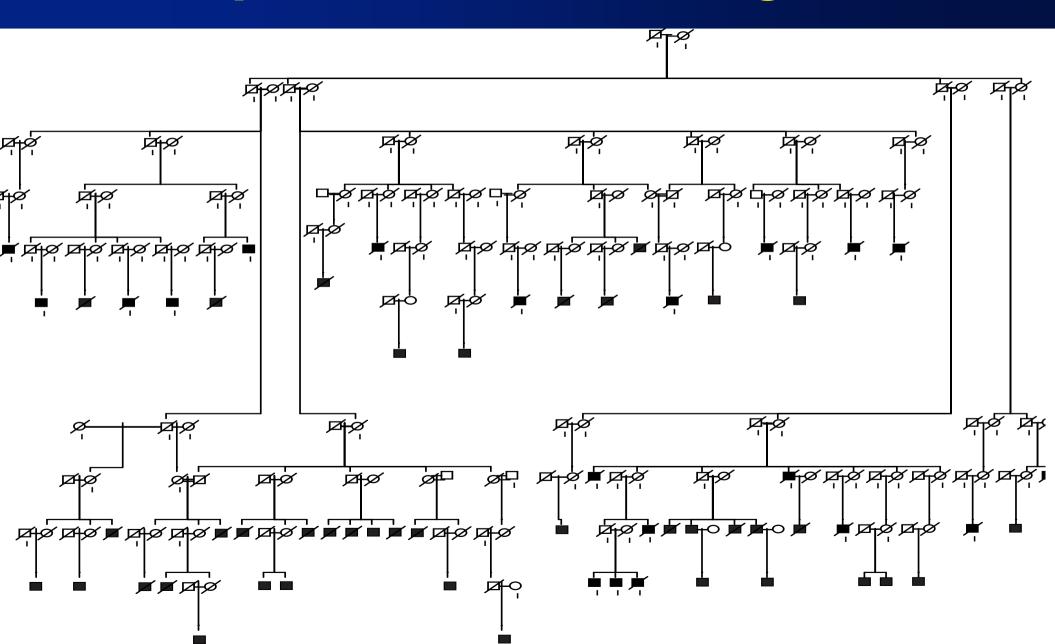
Utah Cancer Registry Data in UPDB

- Selected information for diagnoses from the 1950s to present
- Statewide since 1966

- 55-60% of cancer records link to family records
- Cancer records updated annually

Clinical characteristics and survival data

Sample Utah Prostate Pedigree



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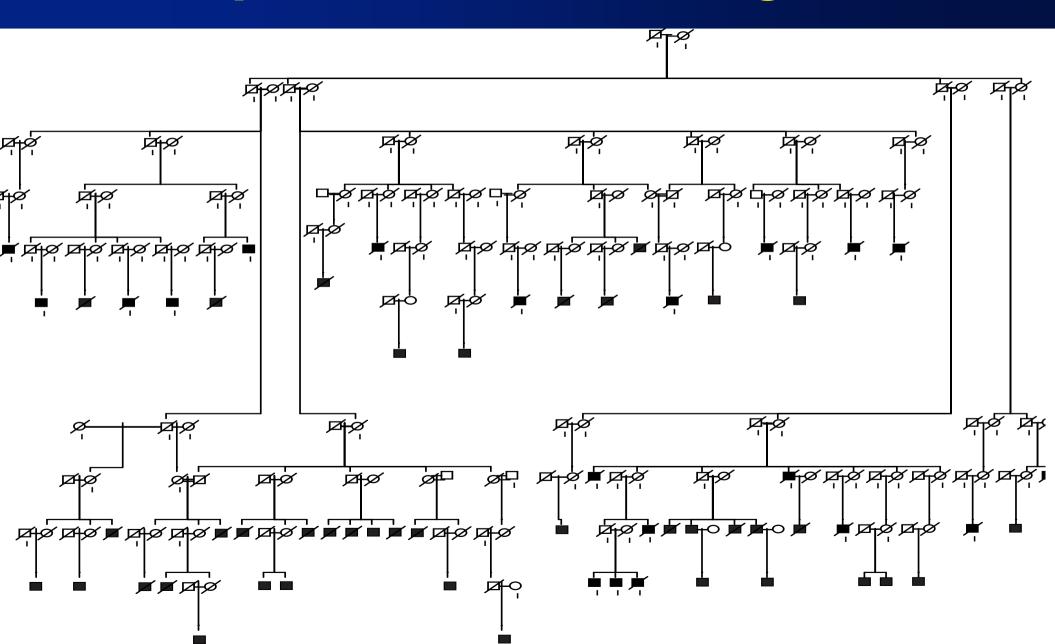
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Genetic Epidemiology High Risk Cancer Pedigrees

<u>Disease</u> Breast Cancer	<u>Time period</u> 1972 - 1992	<u>Pedigrees</u> 490	DNA samples 6215
Colon Cancer	1981 - 1991	272	3993
Melanoma	1986 - 1994	179	2361
Prostate Cancer	1990 - present	273	8491

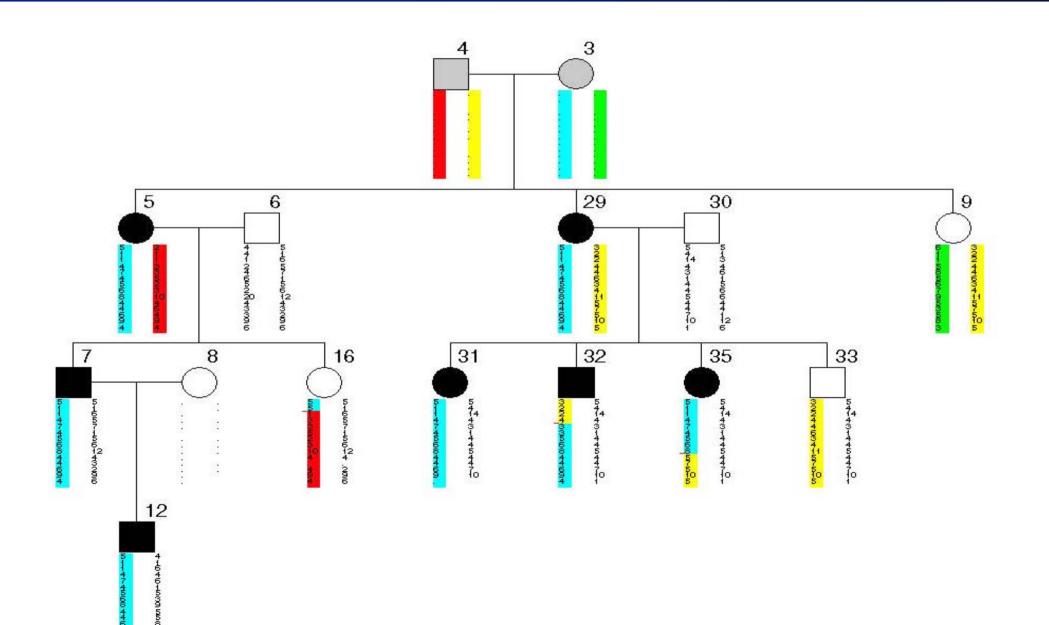
 The Utah pedigree set is the largest total set in the world, with the largest pedigree sizes

Utah Prostate Pedigree Genotyping

Genotyping:	<u>Total</u>
Pedigrees	144
Individuals	3700
Markers	727
Genotypes	1,596,515

genealogy + disease + genotypes

Analyzing Extended Pedigrees to Localize a Gene



Genes Identified by Genetic Epidemiology and Collaborators using UPDB pedigrees

1980	Hemochromatosis
1987	Neurofibromatosis
1988	Alport Syndrome
1994	p16 melanoma gene
1994	BRCA1 breast cancer gene
1996	BRCA2 breast cancer gene
2001	HPC2/ELAC2 prostate cancer gene

+ 245 publications and 38 funded grants

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Cancer Gene Understanding using UPDB

- Familiality studies
 - Heritable component of cancer by site
- Relative Risks in Relatives
 - Clinical utility of family history
- Cancer Associations
 - Phenotypic expression of increased cancer risk

Utah Analysis of Familiality

Measurement of familiality or relatedness in a set of cases

- to test the hypothesis of a heritable component to disease
- are the cases more related than expected?
 - GIF (Genealogical Index of Familiality- Hill et al., 1980)
 - Estimates average relatedness of all possible pairs in a group of cases
 - Significance measured by comparison to the mean GIFs of 1000 sets of matched controls

Utah Analysis of Cancer Familiality

		case	control	
Site	<u>n</u>	GIF	GIF	<u>significance</u>
lip	1243	4.65	2.67	< 0.00001
small intestine	256	4.31	2.68	0.01
prostate	13969	3.48	2.56	< 0.00001
thyroid	1180	3.36	2.04	< 0.00001
melanoma	3798	3.22	2.27	< 0.00001
testis	531	3.21	2.06	< 0.00003
colorectal	8048	3.20	2.56	< 0.00001
stomach	1496	3.18	2.60	<0.00009
lung	4124	3.03	2.57	< 0.00001
lymphoma	3451	2.94	2.37	< 0.00001
breast	10924	2.92	2.42	< 0.00001
ovarian	1643	2.89	2.42	0.0006

Familiality of Prostate Cancer by Clinical Features

	number of		
Group	cases	GIF	<u>significance</u>
By grade:			
Moderately differentiated	6463	2.71	< 0.00001
Poorly differentiated	2872	2.98	< 0.00001
Undifferentiated	207	6.61	< 0.00001
By survival:			
Survivors (> 10 yrs)	2113	4.11	< 0.00001
Non-survivors	874	2.51	0.74

Cancer Relative Risk Estimates

Risk of Prostate Cancer in First Degree Relatives of Prostate Cases

	Number of				
Proband	n	Relatives	(95% CI)	<u>RR</u>	
All prostate	16707	140,008	(1.85,1.96)	1.91	
Early diagnosis	1518	11,448	(2.93,3.51)	3.21	

Prostate Cancer Associations-Increased risks for other cancers in relatives

Cancer Type	<u>Observed</u>	Expected	<u>RR</u>
Urinary/Bladder	624	520	1.20
Breast	2084	1733	1.20
Colon	530	418	1.27
Rectal	468	376	1.25
Leukemia	503	385	1.31
Lip	249	196	1.27
Non-Hodgkin's	561	460	1.22
Stomach	317	244	1.30
Corpus Uteri	599	504	1.19

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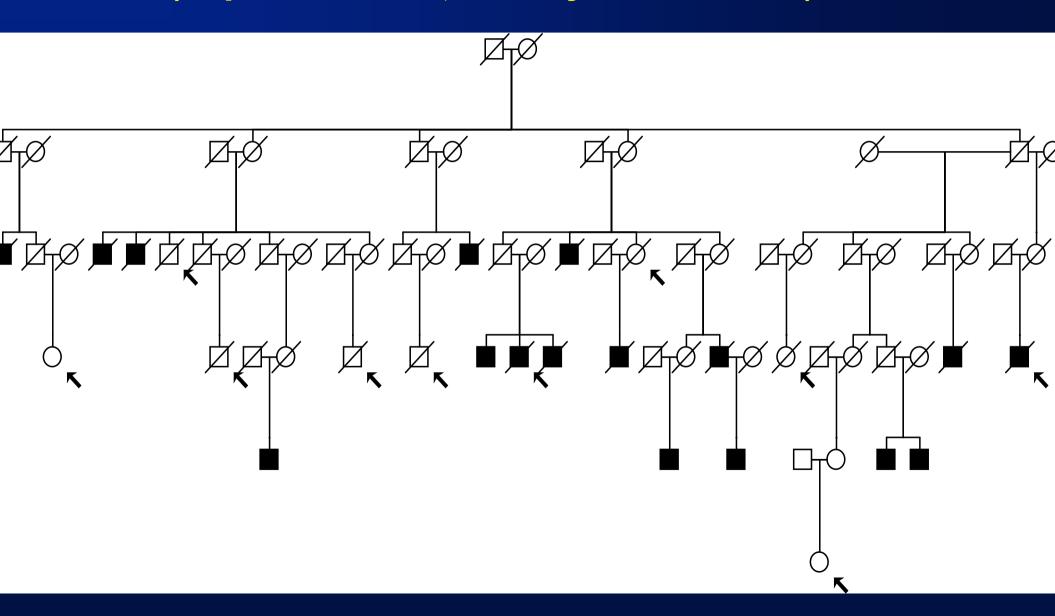
Future of the UPDB/UCR Resource for Cancer Research

Difficult to find predisposition genes for cancer

- Different approaches?
 - More homogeneous pedigrees
 - Co-aggregation of cancer characteristics (survival, grade)
 - Co-aggregation of prostate and other cancer sites
 - Pseudo-Isolate populations in the UPDB*

Irish Isolate Prostate Pedigree

(17 prostate cases, 9 kidney/bladder cases)



Summary

- Variety of population resources for cancer gene identification
 - the Utah resource is unique
 - high quality and quantity UCR phenotypes have been vital
 - genealogy data allows us to apply appropriate study design

 Large genealogical resources with high quality phenotype data allow a multitude of approaches (Skolnick, 1977)

Acknowledgments

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