

THE CENTRE FOR DIABETES RESEARCH

- TEN YEARS OF DISCOVERY -

Grant Morahan

Centre for Diabetes Research
Centre for Systems Genetics



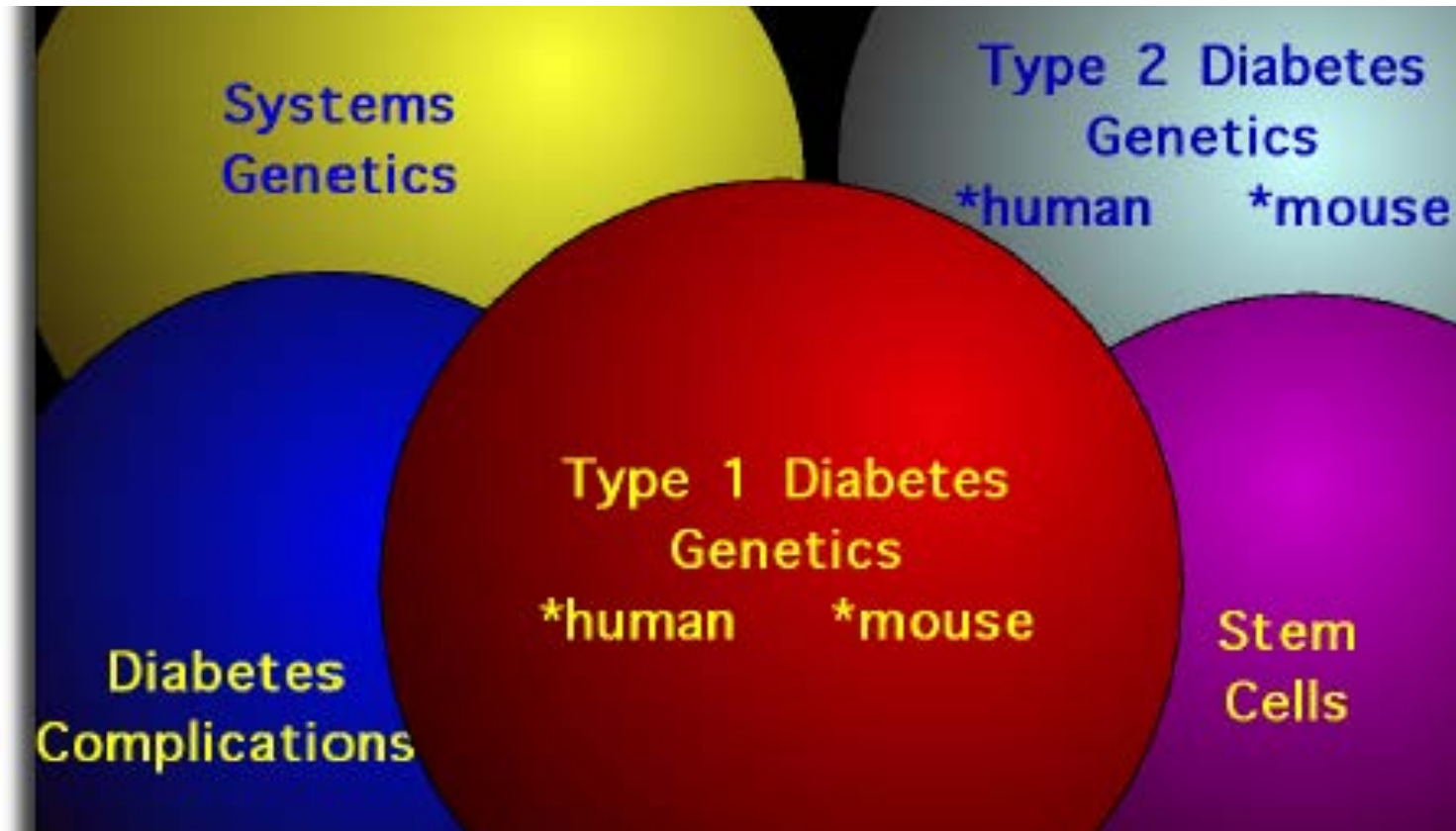
The Centre for Diabetes Research was established in 2005 through a Diabetes Research Foundation of WA (now trading as Diabetes Research WA) fundraising initiative.

The Centre is a world-class facility conducting quality research into diabetes and has won competitive funding from the National Health & Medical Research Council and other funding bodies from around the world. The Centre resides in Perth, Western Australia.

(adapted from Professor Grant Morahan's presentation on 13th November 2013 by Sherl Westlund)

What does the Centre for Diabetes Research do?

The Centre conducts research into many aspects of diabetes. These are the main areas of research.



Why Genetics?

Finding disease genes helps to:

- Better understand the disease
- Identify people at risk
- Develop better treatments

Top 10 discoveries from the Centre for Diabetes Research in the past 10 years

Note:

T1D means type 1 diabetes

T2D means type 2 diabetes

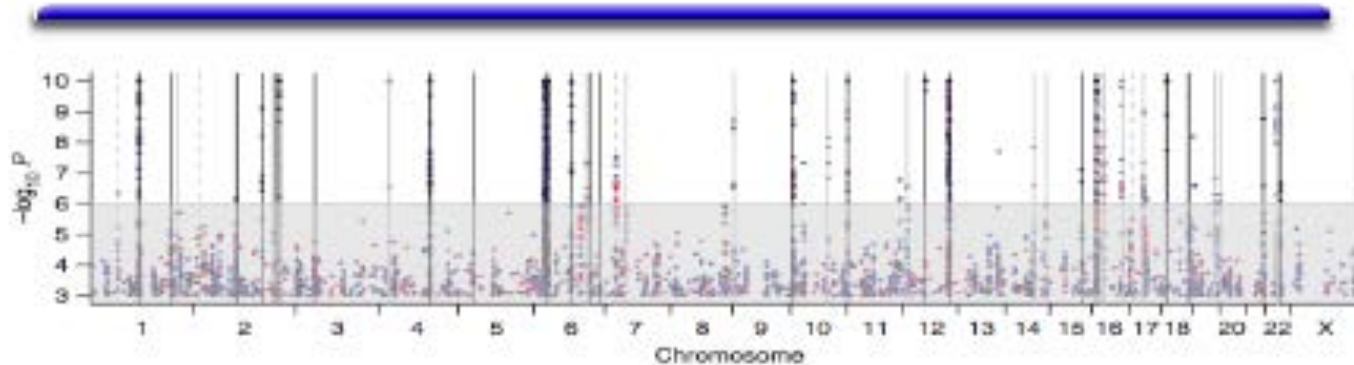
LUPINS IMPROVE T2D

- Reduce Food intake
- Reduce body weight gain
- Increase INS sensitivity
- *Help obese cases lose weight*
- Genetic variation in effects

(INS means insulin)

Researchers at the Centre, and in collaboration with other researchers, have discovered that lupins have a positive effect in controlling hunger and assisting in weight reduction which can improve management of T2D.

DISCOVERY OF 40+ T1D GENES



- T1DGC - recruited 4,000 families
- ACDDR - recruited 3,000 families
- Largest family genetic study ever
- Used in over 700 papers since 2009

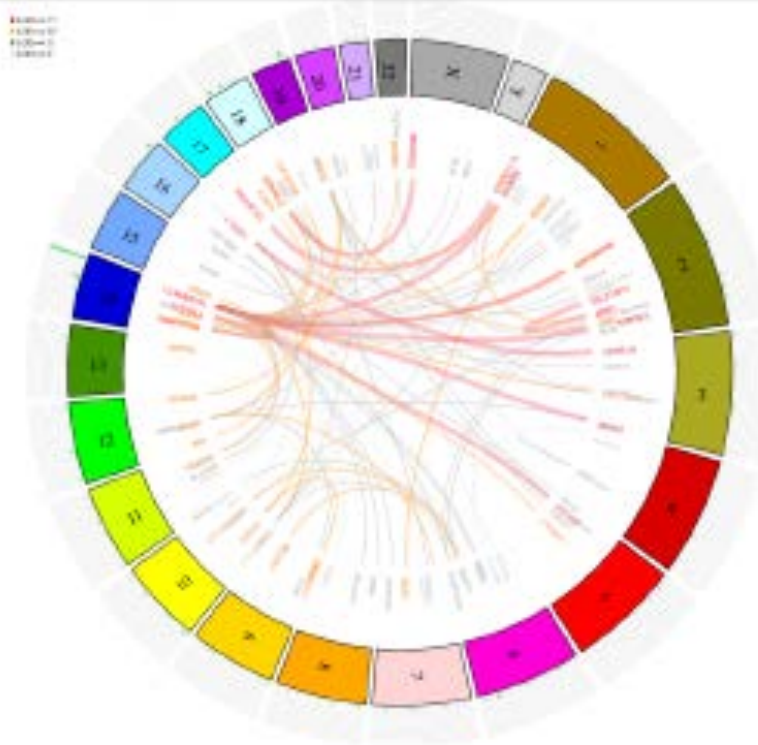
[T1DGC](#) – type 1 diabetes genetic consortium

[ACDDR](#) – Australian Childhood Diabetes DNA Repository.

Systems Genetics

System Genetics is the name given to the study of genes and how they interact by Professor Grant Morahan. This interaction applies to how diseases can develop. You can see the cross-over of gene interaction below.

200 people
x 3 cell types
x 30,000 genes
x 200,000 genetic markers



T1D Genes Control Other Genes

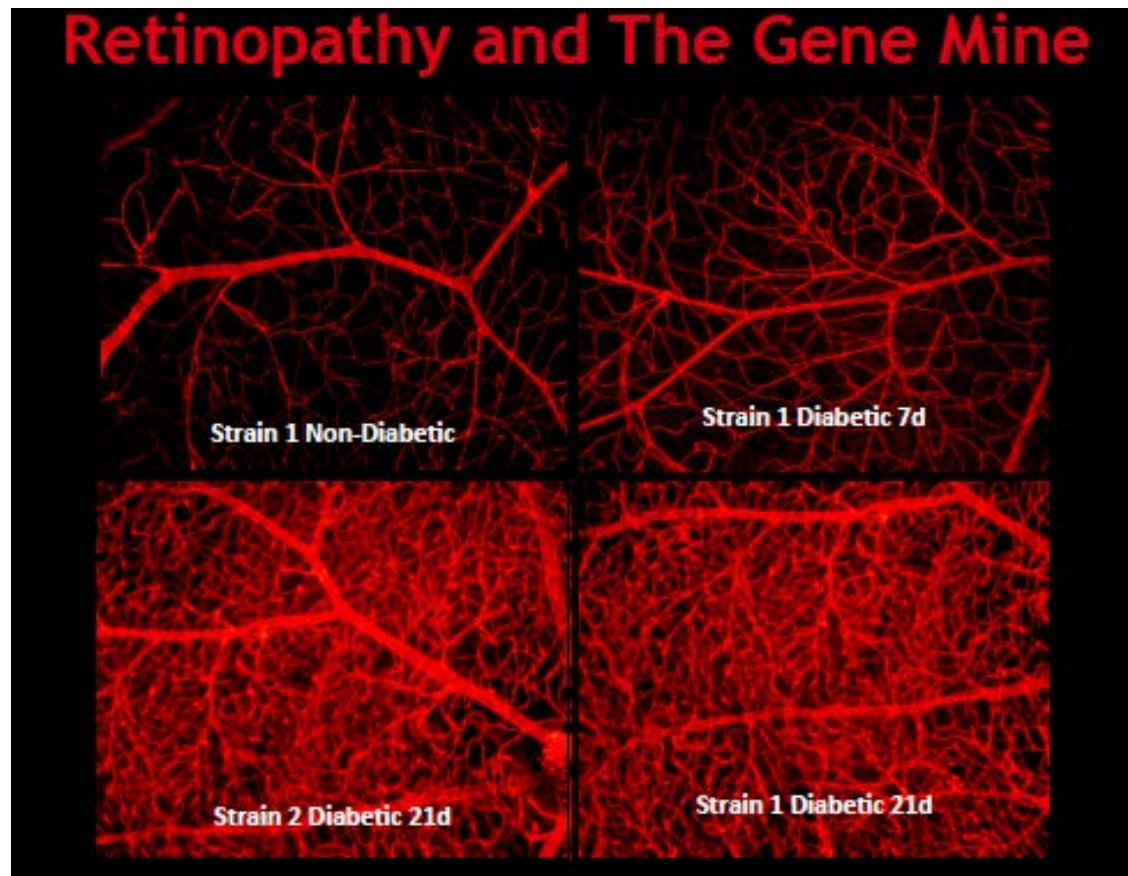
- 💡 Tested 60 T1D genes
- 💡 Only 15 may change proteins
- 💡 25 control expression of nearby genes
- 💡 20 control expression of distant genes

Professor Morahan has tested over 60 T1D genes and discovered that some of these genes affect or control other genes which can impact on health and disease .

Diabetic Retinopathy Model

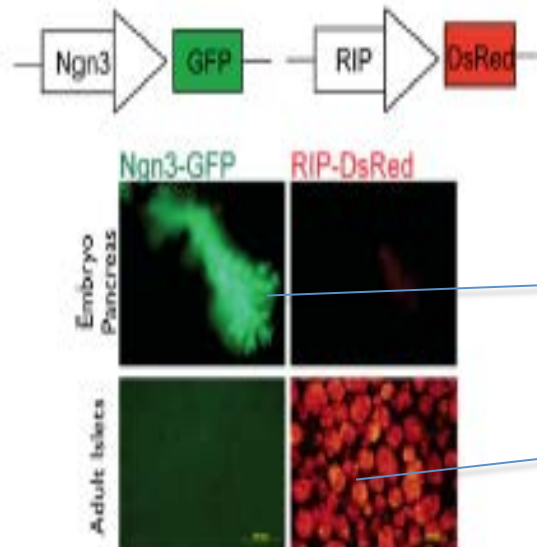
Professor Morahan and his team have now developed a diabetic mouse which can be used to research diabetic retinopathy (blindness). Research will now take place in to the development of better treatments and management in collaboration with other researchers.

You can see the difference between the blood vessels of the retina in the left-hand slide and the other slides due to diabetes. There are many more vessels in the diabetic retina than in the non-diabetic retina.



Beta Cell Production

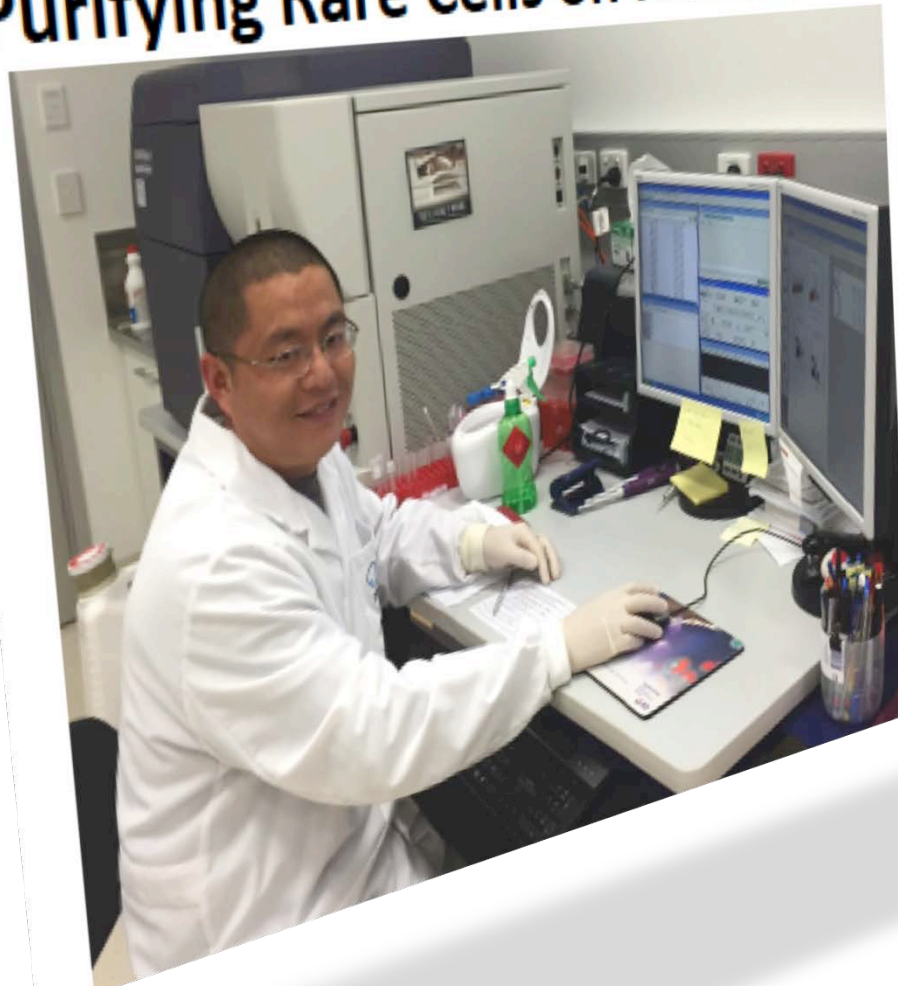
- Two-step method to produce beta cells
- Developed by Fang-Xu Jiang
- Uses double transgenic mice



Beta cells produce insulin which helps convert food into energy. They are destroyed by the immune system in type 1 diabetes. Developing beta cells as a replacement therapy for T1D is the most promising approach for a cure.

In a world first Dr Fang-Xu Jiang at the Centre, has been able to develop beta cells (green) and convert them into insulin producing cells (red). This gives us great hope for a cure.

Purifying Rare Cells on FACS Aria2



For research to be undertaken effectively cells need to be separated and purified.

This machine, the FACS Aria 2, was purchased in 2008 for research at the Centre and is now available for other researchers to use in their work.*

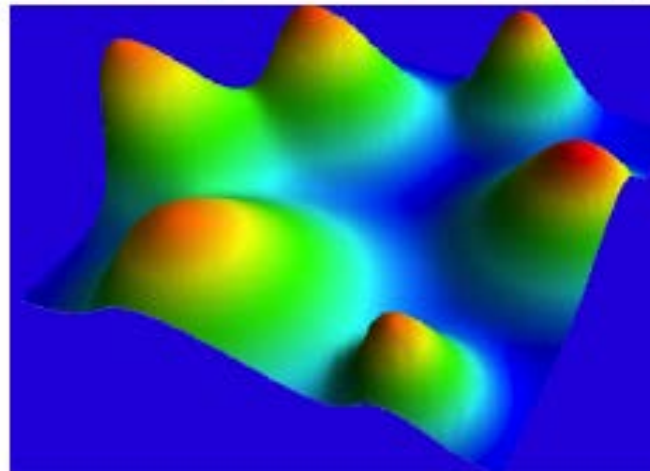
This machine is used in purifying beta cells in search for a cure for diabetes.

* Collectively funded in 2008 by Diabetes Research WA, The University of Western Australia, Diabetes WA and the Western Australian Institute for Medical Research (now Harry Perkins Institute for Medical Research).

Genetic Subtypes of T1D

- Analysed 3,488 T1D probands
 - in 154 dimensions
- Six different genetic subtypes

Proband is the name given to the first family member to be diagnosed or studied.

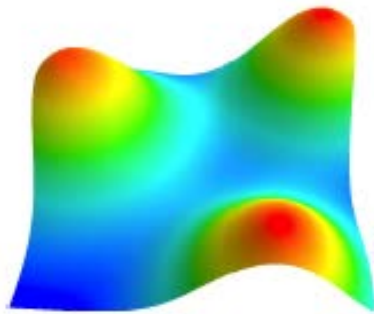


Professor Morahan and his team at the Centre have discovered there are 6 subtypes of T1D which have different clinical features. This might explain why some people develop complications like kidney disease and others don't.

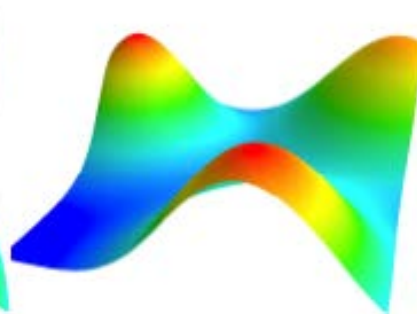
Profiles of T1D Subtypes

Subtype	1	2	3
DR	4/x	3/x	3/4 Female
Most ab	IA2	GAD65	All (except IA2)
Least ab	Tg	IA2, ATPase ab	–
Highest risk of:	vitaligo	Coeliac,Nephropathy	thyroid; hypo; coma
Lowest risk of:	–	–	Nephropathy
Subtype	4	5	6
DR	3/4 Male	3/4 or 4/x	x/x
Most ab	–	–	–
Least ab	–	GAD65	All but IA2, GAD
Highest risk of:	Age at onset; coma; nephropathy	–	Hypothyroid
Lowest risk of:	Thyroiditis; vitaligo	–	Coeliac

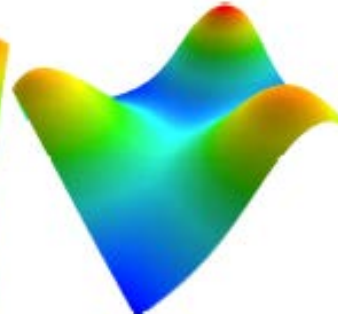
Simplifying Complex Diseases



Heart Disease



Breast Cancer



Type 2 Diabetes

Also: diabetic complications, Alzheimer's, venous thrombosis, melanoma ...

Research methods developed at the Centre can now be applied to other diseases so that new understandings of other diseases like breast cancer and melanoma are possible. This may lead to improved management and treatment of these diseases.

Type 2 Diabetes Subtypes

Tim Davis, Wendy Davis,
Fremantle Diabetes Study; n=1,244

Trait	Subtype 1	Subtype 2	Subtype 3	P
Kidney Disease	50%	38%	47%	0.0004
Heart Disease	47%	49%	65%	6E-07
Death or MI	28%	25%	36%	0.0007

Research at the Centre has discovered there are 3 subtypes of T2D which may have clinical features. This allows for better treatment and management of type 2 diabetes.

Predicting T1D Risk

- Tested TrialNet participants
- Define genetic risk signature

TrialNet is a world-wide study network dedicated to the study of type 1 diabetes

Professor Morahan and his team have joined with Dr Joey Kaye at Sir Charles Gairdner Hospital to develop a test that could indicate a person's risk of developing T1D in siblings of a person with T1D. This test will also research the ability to predict complications developing.

The Gene Mine

- World-leading genetic resource
- Captures >90% of common species variation
 - DNA variants ~200 bp
 - 16,182 genes encode different proteins
- Highly variable in hundreds of tested traits
- Rapid gene discovery
- New animal models
- Disease prevention

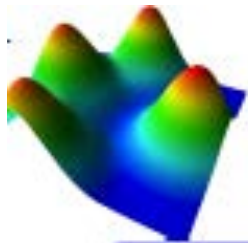
The Gene Mine is a revolutionary new mouse genetic resource developed by Professor Grant Morahan.

This tool allows rapid discovery of disease genes and is important in the understanding of the molecular basis of how diseases occur.

Predicting Disease Outcomes

Research at the Centre has been able to use the methods developed for diabetes research to predict outcomes for other diseases. This research will pave the way for better treatments earlier on following diagnosis.

Predicting Melanoma Survival



Predicting Heart Attack

Centre for Diabetes Research Staff



2005 – 2014

- Brought over \$15 million (more with T1DGC)
 - NHMRC (3 Programs, 2 Projects); NIH
- Employed 55 staff, students
- Over 100 scientific papers
- Two patents
- Four Ph.D. Students
- Founded two companies
- Established world-leading Gene Mine

2015 –

- Validate genetic prediction tests
 - diabetic complications
 - T1D risk
 - Hypoglycemic unawareness
- Test compounds to prevent retinopathy
- Establish Clinical Trials Centre
 - Link 4 WA adult hospitals; JDRF
- Develop beta cell production methods
- Discoveries from The Gene Mine

Thanks

Diabetes Research
Western Australia

