Symposium 5b
Patient engagement and return of genomic data

Viking Genes: Return of actionable genetic research results to Scottish cohort participants

Dr Shona M. Kerr

Nordic Biobank Conference 2022

Outline of Today's Talk

- Introduction to the **Viking Genes** Biobank
- Recruitment, engagement & **involvement** of >**8,000 participants** with ancestry from the **Northern Isles of Scotland**
- Progress towards **return** of actionable genetic results
- **Framework** for other cohorts and biobanks considering return of results

“Viking Genes” – The Northern Isles of Scotland

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People from Orkney & Shetland have the highest degree of “Norse blood” in the British Isles & Ireland

PNAS

The genetic landscape of Scotland and the Isles

Edmund Gilbert[a,b], Seamus O'Reilly[c], Michael Merrigan[c], Darren McGettigan[c], Veronique Vitart[d], Peter K. Joshi[e], David W. Clark[e], Harry Campbell[e], Caroline Hayward[d], Susan M. Ring[f,g], Jean Golding[h], Stephanie Goodfellow[i], Pau Navarro[d], Shona M. Kerr[d], Carmen Amador[d], Archie Campbell[j], Chris S. Haley[d,k], David J. Porteous[j], Gianpiero L. Cavalleri[a,b,1], and James F. Wilson[d,e,1,2]

[a]School of Pharmacy and Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin D02 YN77, Ireland; [b]FutureNeuro Research Centre, Royal College of Surgeons in Ireland, Dublin D02 YN77, Ireland; [c]Genealogical Society of Ireland, Dún Laoghaire, Co. Dublin A96 AD76, Ireland; [d]Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, Scotland; [e]Centre for Global Health Research, Usher Institute, University of Edinburgh, Edinburgh EH8 9AG, Scotland; [f]Bristol Bioresource Laboratories, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol BS8 2BN, United Kingdom; [g]Medical Research Council Integrative Epidemiology Unit at the University of Bristol, Bristol BS8 2BN, United Kingdom; [h]Centre for Academic Child Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol BS8 1NU, United Kingdom; [i]Private address, Isle of Man IM7 2EA, Isle of Man; [j]Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, Scotland; and [k]The Roslin Institute and Royal (Dick) School of Veterinary Sciences, University of Edinburgh, Edinburgh EH25 9RG, Scotland

VIKING I cohorts – clinic recruitment from 2005 – 2015

~4,000 participants
from Orkney or Shetland

Consent for feedback of phenotype from clinic visit, not for genetic results

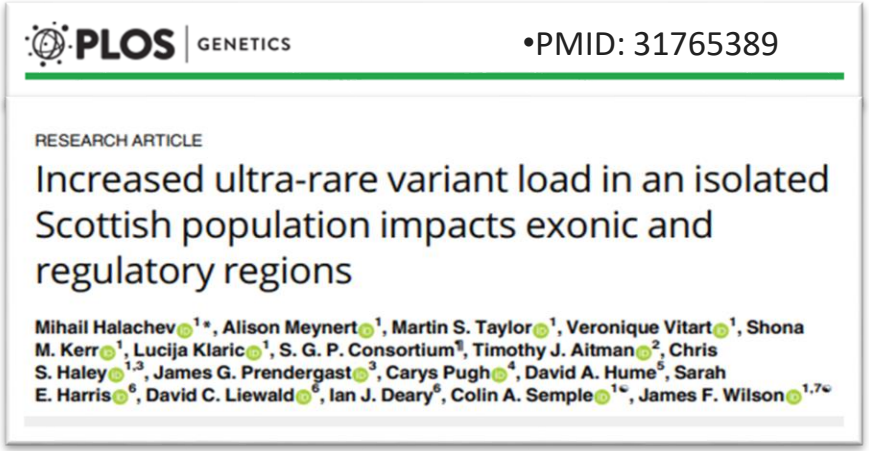
ORCADES VIKING HEALTH

- Have supported hundreds of research papers
- Blood collected in clinics for plasma, serum, RNA and DNA – "multiomics"
- The DNA samples were genotyped, then some WGS and finally all exome sequenced
- Linkage to NHS data

www.ed.ac.uk/viking

VIKING cohorts – rare genetic variants

Research using the increasingly detailed genetic data shows a different pool of rare gene variants compared to cosmopolitan populations



PLOS GENETICS

•PMID: 31765389

RESEARCH ARTICLE

Increased ultra-rare variant load in an isolated Scottish population impacts exonic and regulatory regions

Mihail Halachev[1]*, Alison Meynert[1], Martin S. Taylor[1], Veronique Vitart[1], Shona M. Kerr[1], Lucija Klaric[1], S. G. P. Consortium[¶], Timothy J. Aitman[2], Chris S. Haley[1,3], James G. Prendergast[3], Carys Pugh[4], David A. Hume[5], Sarah E. Harris[6], David C. Liewald[6], Ian J. Deary[6], Colin A. Semple[1☯], James F. Wilson[1,7☯]

Some rare variants are medically relevant.
And some of those are “actionable”

Actionable finding: a gene change that is linked to a condition or disease that can be prevented or improved by (NHS) treatment.

Actionable variant = AV

An AV that increases risk of sudden death

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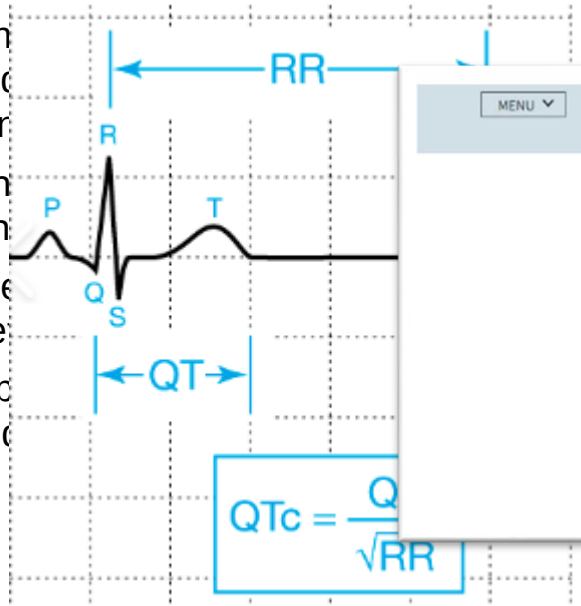
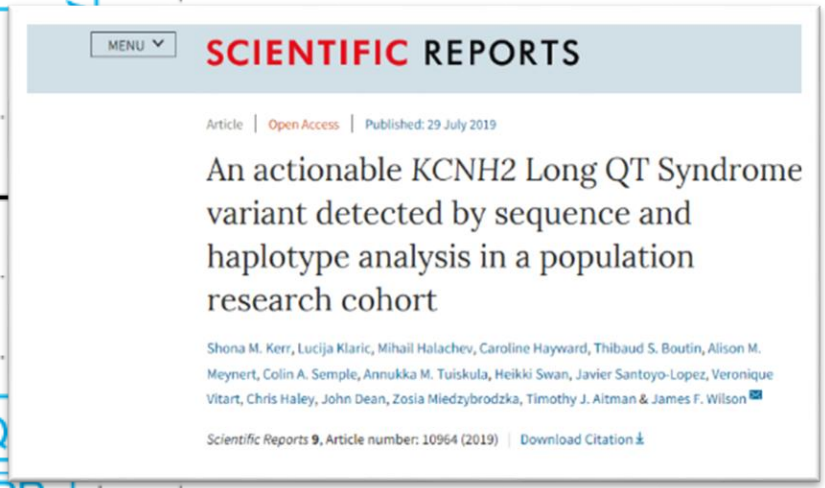
- Analysis from WGS of 5 action
  LQTS carriers from Shetland: c
  relationship from a common ar
- Carriers in “Family B” not conn
  A” in recorded pedigree or gen
- Therefore Family B was not ide
  cascade testing in a clinical se
- We returned results via GPs (p
  based on ECG data (prolonge
  phenotype)




MENU

SCIENTIFIC REPORTS

Article | Open Access | Published: 29 July 2019

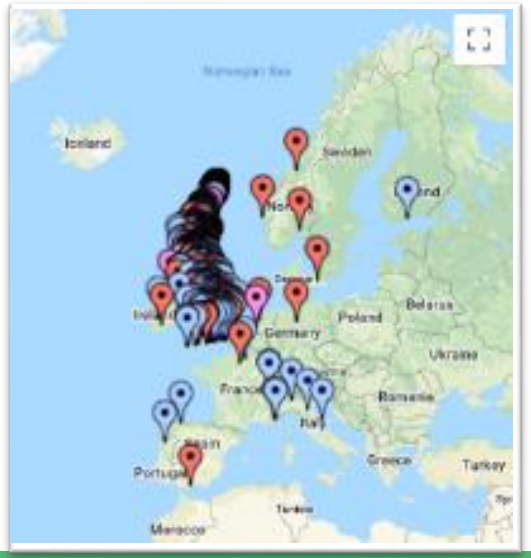
An actionable *KCNH2* Long QT Syndrome variant detected by sequence and haplotype analysis in a population research cohort

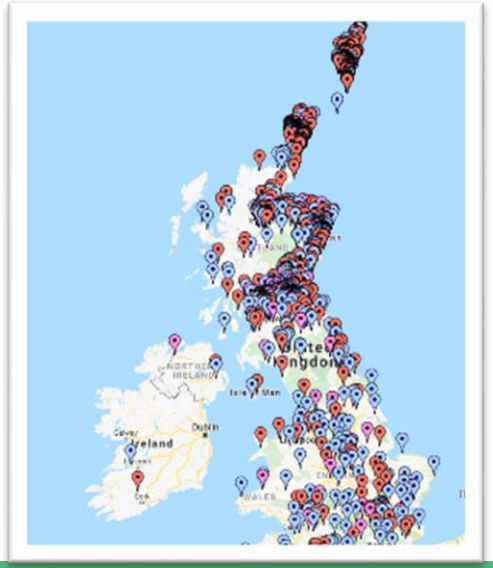
Shona M. Kerr, Lucija Klaric, Mihail Halachev, Caroline Hayward, Thibaud S. Boutin, Alison M. Meynert, Colin A. Semple, Annukka M. Tuiskula, Heikki Swan, Javier Santoyo-Lopez, Veronique Vitart, Chris Haley, John Dean, Zosia Miedzybrodzka, Timothy J. Aitman & James F. Wilson

Scientific Reports **9**, Article number: 10964 (2019) | Download Citation

VIKING II cohort - recruitment launched January 2020

- VIKING II is an online study, no clinics
- Online consent & questionnaire, “spit-and-post” saliva collection for DNA
- Eligibility: two or more grandparents Orkney or Shetland, >4,000 new volunteers
- Electronic health record linkage (all three Viking Genes cohorts ~8,000 people) “longitudinalisation”
- REC-approved consent for return of selected actionable genetic results
- Worldwide recruitment

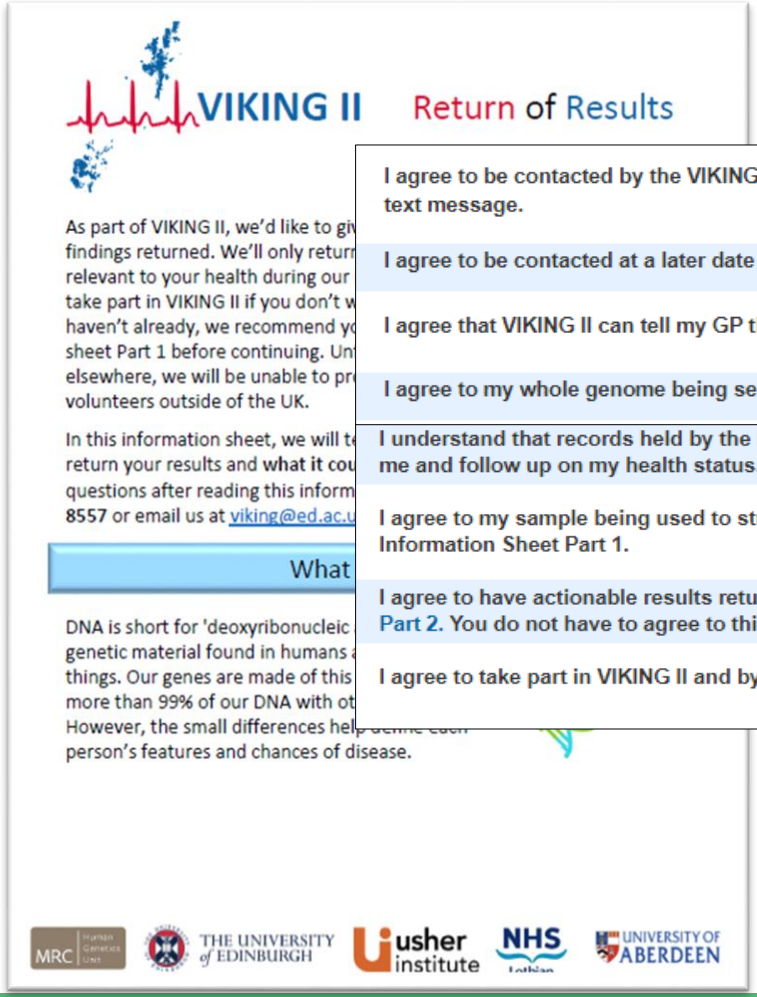




VIKING II Participant Locations

Northern Isles 46.3% Rest of Scotland 35%

Rest of UK 10.2% Rest of World 8.5%



I agree to be contacted by the VIKING II team about taking part in VIKING II, including by reminder emails and a reminder text message.	☑
I agree to be contacted at a later date in connection with future ethically approved studies.	☑
I agree that VIKING II can tell my GP that I am taking part, for their records.	☑
I agree to my whole genome being sequenced as described in the Participant Information Sheets.	☑
I understand that records held by the NHS including the Central Register for Scotland may be used to keep in touch with me and follow up on my health status.	☑
I agree to my sample being used to study … Information Sheet Part 1.	☑
I agree to have actionable results returned … Part 2. You do not have to agree to this to	◉ Yes ○ No
I agree to take part in VIKING II and by che…	☑

Viking Genes - Return of Results

Close | Print | Export

Total	Results returned to me
104	No
5013	Yes

VIKING II: DNA Extraction & Sequencing

clinical research facility EDINBURGH

Need sequence data to find actionable variants

DNA extractions delayed due to covid research prioritisation by the core lab, which in turn delayed the sequencing

Actionable BRCA1 variant found in 20 participants of Westray descent – a founder mutation

Classification: Pathogenic in ClinVar database, familial breast-ovarian cancer

Nearly 500-fold higher variant frequency in Orkney compared to UK Biobank

Clinical case study meets population cohort: Identification of a *BRCA1* pathogenic founder variant in Orcadians

Shona M. Kerr, Emma Cowan, Lucija Klaric, Christine Bell, Dawn O'Sullivan, David Buchanan, Joseph J. Grzymski, Regeneron Genetics Center, Cristopher V. van Hout, Gannie Tzoneva, Alan R. Shuldiner, James F. Wilson, Zosia Miedzybrodzka

doi: https://doi.org/10.1101/2022.07.18.22276644

Dataset	Description	Number of Genomes	Carriers of BRCA1 p.val1736ala variant	Cases of HBOC (females)
gnomAD v2.1.1	Unrelated individuals from genetic studies	125,748 exomes and 15,708 genomes	0	-
Viking Health Study Shetland	Isolate population cohort from Shetland, UK	2,106 exome sequences	0	-
ORCADES	Isolate population cohort from Orkney, UK	2,090 exome sequences	20: 13 males and 7 females	1
UK Biobank	Cosmopolitan population cohort from UK	200,000 exome sequences	4: 1 males and 3 females	1

Actionable genetic variants: ~1 - 4% of populations

- Most genetic AVs act dominantly, i.e., when present in a single copy (heterozygote)
- Many are in genes that can affect risk for cardiovascular conditions, or cancer
- No return of results of clinically uncertain significance
- By definition, return of AV results is **not** the same as sharing all genetic data with volunteers:

  - Does not disclose genetic variants predisposing to conditions with no treatment
  - Does not disclose variants that act recessively
  - Reduces issues of family structure e.g., non-paternity
  - New AVs will continue to emerge, therefore long-term engagement with volunteers is important

Lewis *et al. Genome Medicine* (2021) 13:115
https://doi.org/10.1186/s13073-021-00928-5

Genome Medicine

COMMENT Open Access

An international policy on returning genomic research results

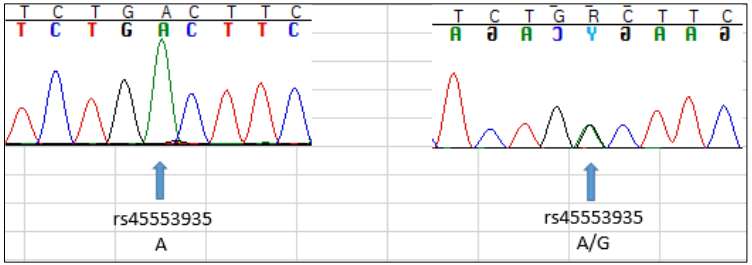
Anna C. F. Lewis[1,2,3*], Bartha Maria Knoppers[4] and Robert C. Green[2,3,5,6]

Abstract

The Global Alliance for Genomics and Health has approved a policy for the return of clinically actionable genomic research results, the first such policy approved by an international body. The policy acknowledges the potential medical benefits to millions of individuals who are participating in genomics research. It ties the pace of implementation to each country's clinical standards, including for the return of secondary findings, and urges funders to set aside resources to support responsible return.

Checklist of steps for RoR

- Consider which results to return
- Develop a plan for return of results
- Obtain participant informed consent
- Collect and analyse data
- Confirm results
- Disclose research results
- Follow-up and monitor



Vears *et al*, manuscript in preparation, Isabelle Budin-Ljsne

Return of results is in partnership with UK NHS Clinical Geneticists

Prof. Zosia Miedzybrodzka

Dr. John Dean

VIKING Genes home

About Us

Volunteer Stories

- Ingrid's Story
- Dot's Story
- Andrea's Story
- Garry's Story
- Heather's Story
- Helga and Ingrid's Story
- Lena's Story
- Dawn's Story
- Fiona's Story
- Sonya's Story

Home > VIKING Genes > About Us > Volunteer Stories

Contact us

Volunteer Stories

Hear from our volunteers. Find out why they joined and what they enjoyed most about their experience.

Ingrid's Story

Ingrid is a Viking Health Study - Shetland volunteer. When she heard we were looking for new volunteers for VIKING II, she shared her story, showing the benefits of receiving actionable genetic results.

Dot's Story

Dot came to visit us on Friday 13th March 2020. It might be an unlucky day for some but she enjoyed her visit and shares her experience here.

Andrea's Story

Andrea was originally born in Edinburgh and her family has a very interesting history related to our studies. Read more here.

Garry's Story

Garry has two grandparents from Orkney and, with the help of relatives, is discovering more about his family tree. Read his story here.

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Ingrid's Story

Ingrid is a Viking Health Study - Shetland volunteer. When she heard we were looking for new volunteers for VIKING II, she shared her story, showing the benefits of receiving actionable genetic results.

I have lived in Aberdeenshire for over 30 years, but prior to that was brought up in Lerwick, Shetland. Both sides of my family are from Shetland, for as far back as we can trace. My parents both took part in the Viking Health Study - Shetland and received their results. When I heard they were calling for additional volunteers I thought I would do it too. I thought it would be interesting to take part, predominantly as it looked like a free medical!

I received a great report on my overall health and I filed it away at the time thinking I would never see it again. However, several years later I was contacted by my GP, as they had received notification of a potentially rare genetic mutation via the Viking Health Study - Shetland. An ECG, a full heart MRI and some genetic testing later, it was discovered I had Long QT. It's a genetic condition which can cause an erratic heartbeat but one that is very difficult to spot using standard medical tests. Through genetic testing we have since discovered my father and my 9 year old daughter both have the same genetic mutation. Thankfully no one else in our immediate family was found to be carrying this gene.

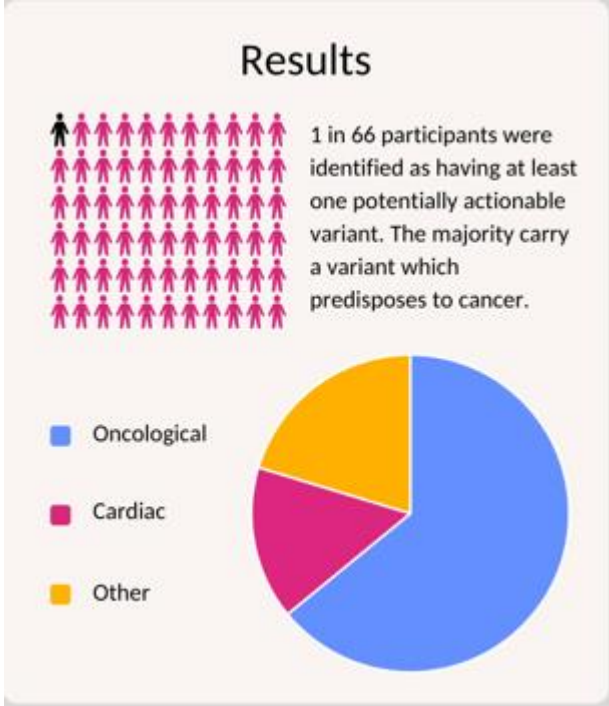
Both myself and my daughter now take daily beta blockers to control our heart rhythm and see a cardiologist every 6-12 months. Neither of us have ever had any symptoms and live very fit and healthy lives. We will never be certain, but it is possible that taking part in this survey has saved our lives. Long QT is the type of condition that you don't often find out you have until it is too late. Thankfully with the medication we are on we are both able to continue to do all the things we love, including running and, in the case of my daughter, football and swimming. I can't recommend this survey enough, you just never know what you might find out!

Ingrid was told about Long QT thanks to research conducted by the team in 2018, and published in 2019. If you'd like to read more about this research, visit the link below.

Rare Ancestral Variant found in VIKING Health Study

Summary & Next Steps

- Offer consent for RoR to existing biobank participants
- Finish analyses of research data (exome sequence) in Viking Genes to identify actionable findings
- Agree list of variants to be returned (clinical input)
- Implement Return of Results (~120 people in 8,000 Viking Genes participants)
  - Research results, so verify by a different analysis method
  - **We send a letter, with an invitation to find out more**
- NHS will offer counselling, and take a new blood sample for analysis
- Materials & experience from Viking Genes should be of wider value:
  - Both consent at recruitment, and re-consent of existing cohorts
  - Participant engagement and involvement, benefit sharing
  - In line with international policy and the wishes of participants



VIKING Genes

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Viking Genes Team –
Rachel Edwards, David Buchanan and Prof Jim Wilson

NHS Grampian Clinical Genetics
Dr Lucija Klaric

Clinical Research Facility, University of Edinburgh

The Volunteers!

Social Media:

- @vikinggene
- @vikinggenes
- @viking_genes

UKRI MRC Human Genetics Unit

THE UNIVERSITY of EDINBURGH

Thank you!

Email: Shona.kerr@ed.ac.uk

@shona_kerr