ISRCTN16294731 https://doi.org/10.1186/ISRCTN16294731

Can common differences in our genes explain why some people are more sensitive to pain than others?

Submission date
02/11/2021

Recruitment status
No longer recruiting

Registration date
25/11/2021

Overall study status
Completed

Last Edited
14/01/2022

Condition category
Other

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
We know that genes influence our sensitivity to pain, but we do not have a full understanding of how this happens - which genes are important and why?

Who can participate?
We are recruiting participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort who have specific, common, changes in a gene heavily implicated in pain sensitivity call Transient Receptor Potential A1 (TRPA1).

What does the study involve?
We will invite participants to take part, based upon their known genetic information i.e. if they have or do not have these common changes in their TRPA1 gene. We will then carefully determine their pain sensitivity using quantitative sensory testing. This includes determining their heat and cold detection thresholds and pain thresholds, their mechanical detection thresholds, and their mechanical (punctate and pressure) pain thresholds. We will then apply 10% cinnamaldehyde, an activator of TRPA1, to their forearm for 20 minutes, measure any changes in blood flow and then repeat the sensory testing.

What are the possible benefits and risks of participating?
There are some risks associated with participating. Some pain will be experienced, though this will be minimized. The stimuli, particularly the cinnamaldehyde, may cause some redness of the skin which will settle on its own. Any sensations evoked by the cinnamaldehyde can be reduced by gently cooling the affected area.

Where is the study run from?
University of Bristol (UK)

When is the study starting and how long is it expected to run for?
November 2018 to January 2022

Who is funding the study?
Above and Beyond, the University Hospitals Bristol Charity, via their Neurosciences and Mental Health Legacies Call. Grant reference ABL-2019-20-10.
The UK Medical Research Council and Wellcome (Grant ref: 21765/Z/19/Z) and the University of Bristol provide core support for ALSPAC.
Individual team members are supported by the MRC (MC_UU_00011) and the University of Bristol, Wellcome Trust (202802/Z/16/Z) and Cancer Research UK (CRUK) Integrative Cancer Epidemiology Programme (C18281/A29019).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
B3236

Study information

Scientific Title

Evaluating the association of TRPA1 gene polymorphisms with pain sensitivity: A protocol for an adaptive recall by genotype study.

Study objectives
Individuals homozygous for common (MAF>1%) SNPs in TRPA1 will have altered acute pain sensitivity as demonstrated by Quantitative Sensory Testing.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/10/2019, ALSPAC Ethics and Law Committee (Children of the 90s, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, UK; +44 (0)117 331 0010; alspac-ethics@bristol.ac.uk), ref: 94082

Study design
Single centre adaptive recall by genotype study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
The association of TRPA1 gene polymorphisms with pain sensitivity

Interventions
Five TRPA1 SNPs known to introduce missense mutations and with minor allele frequencies of >1% hypothesized to impact TRPA1 function will be investigated. The effect of these five SNPs will be assessed in three groups due to the high linkage disequilibrium between two pairs of minor alleles. QST results from the individuals in these three test groups will be compared to those of a reference group who are homozygous for the major (ancestral) allele at all five SNPs. The results will be subject to planned interim assessments for futility to alter recruitment if there is low probability of success of detecting a phenotype for a given allele until a maximum of 100 participants have been assessed. Heat pain threshold is the primary outcome.

The SNPs of interest were rs7819749, rs959976 with rs920829, rs16937976 with rs13268757 (dbSNP build 154, GRCh38) and a control group of individuals homozygous for all five major alleles. Investigators and participants will remain blind to genotype throughout the recruitment and data collection phases of the study.

The participants will be assessed using quantitative sensory testing (QST) before and after sensitisation by topical application of 10% cinnamaldehyde (a known activator of TRPA1). QST paradigms are based upon the DFNS protocol, streamlined in line with the primary hypothesis to omit some non-nociceptive assessments.

Intervention Type
Genetic

Primary outcome(s)

Measured before and after 20 minute topical application of 10% cinnamaldehyde in ethanol: Heat pain threshold measured using a thermode (Medoc TSA-II, Medoc, Israel, or similar) on the right volar forearm. The temperature of the thermode will change at 1°C per second until the participant reports either detection of temperature change, or detection of pain via a mouse click. The thermode then returns to a neutral temperature of 32°C. The first trial will be discarded as an acclimatisation and then followed by 3 experimental repeats.

Key secondary outcome(s))
Measured before and after 20 minute topical application of 10% cinnamaldehyde in ethanol:
1. CDT, cold detection threshold measured using the same method as the heat threshold with a cooled thermode
2. WDT, warm detection threshold measured using the same method as the heat threshold
3. CPT, cold pain threshold measured using using the same method as the heat threshold with a cooled thermode

4. MDT, mechanical detection threshold
5. MPT, mechanical pain threshold
6. MPS; mechanical pain sensitivity
Thresholds for innocuous mechanical stimuli will be assessed using calibrated von Frey filaments (TouchTest; Stoelting, USA) via the method of levels. Mechanical pain thresholds, again via the method of limits, and stimulus response curves will be assessed using calibrated punctate needle stimulators (PinPricks; MRC Systems, Germany). For the stimulus response curve participant numerical pain ratings from 0 (no pain) to 100 (worst imaginable pain), will be assessed 5 times with 7 filaments exerting forces from 8 to 512mN presented in a randomised manner

7. Brush, presence or absence of brush allodynia measured with 5 standardised brush strokes (SenseLab; via MRC Systems, Germany)
8. Pressure, deep pressure pain threshold measured using an algometer (Somedic, Sweden) applied over the muscles of the right volar forearm
9. Axonal flare in response to cinnamaldehyde will be measured using full-field laser perfusion imaging (FLPI) of the target area of skin (moorFLPI-2; Moor Instruments)

Completion date
01/01/2022

Eligibility

Key inclusion criteria
Participants within the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort who are a regionally representative cross-sectional population aged around 30 years (with a correspondingly relatively low incidence of chronic pain).

Participant type(s)
Other

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Neurological disorders including peripheral neuropathy
2. Regular use of analgesics
3. Any pain medication taken within 24 hours of QST
4. Pregnancy
5. Acute or Chronic pain conditions
6. Severe anxiety/depression
7. Allergy to cinnamon, mustard, alcohol / chlorhexidine wipes, latex.
8. Use of non-prescribed or recreational drugs (assessed by questionnaire).

Date of first enrolment
27/01/2020

Date of final enrolment
31/12/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Bristol
Oakfield House
Bristol
United Kingdom
BS8 1TD

Sponsor information

Organisation
University of Bristol

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Charity

Funder Name
Above and Beyond, the University Hospitals Bristol Charity, via their Neurosciences and Mental Health Legacies Call. Grant reference ABL-2019-20-10

Funder Name
University of Bristol

Alternative Name(s)
Universitas Bristolliensis, bristoluniversity, bristoluni

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		12/01/2022	14/01/2022	Yes	No
Participant information sheet	version 6	09/09/2019	04/11/2021	No	Yes
Protocol (preprint)		01/12/2020	04/11/2021	No	No