Exploring bleeding risk and platelet function combined with multiple omics techniques in 22q11.2 deletion syndrome

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- To assess platelet (dys)function in adults with 22q11.2DS and its association with bleeding history.- To identify alterations in metabolic pathways in 22q11.2DS that may be of relevance to mechanisms underlying neurodevelopmental and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Platelet disorders
Study type	Observational invasive

Summary

ID

NL-OMON55192

Source
ToetsingOnline

Brief title
Platelet function in 22q11.2DS

Condition

- Platelet disorders
- Chromosomal abnormalities, gene alterations and gene variants
- Schizophrenia and other psychotic disorders

Synonym
DiGeorge syndrome, Velocardiofacial syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: 22q11.2 deletion syndrome, Blood platelets, multi-omics, Schizophrenia

Outcome measures

Primary outcome

- Bleeding risk score (ISTH-BAT questionnaire).

- Complete blood count (including platelet count) and MPV.

- Platelet aggregation and (functional) flowcytometry.

- Flow chamber results with respect to platelet binding to coated surfaces (in bright field view), P-selectin expression, fibrinogen binding and phosphatidyl serine (PS) exposure.

- Global scale quantitative and qualitative RNA differences (transcriptomics).

- Global scale quantitative metabolite differences (metabolomics).

Secondary outcome

- correlation between blood platelet function and age

Study description

Background summary

22q11.2 Deletion syndrome (22q11.2DS) is caused by recurrent hemizygous microdeletions on chromosome 22q11.2, encompassing up to 90 genes. This syndrome is characterized by a multi-organ disorder with a variable phenotype, intellectual disability, cognitive deterioration, schizophrenia, early-onset Parkinson*s disease, recurrent epistaxis, and macrothrombocytopenia; ~30% of the adults with 22q11.2DS have thrombocytopenia (<150,000 platelets per mL). Importantly, platelets have a critical role in haemostasis. Also, they show similarities to neurons concerning several morphologic and biochemical characteristics, are easier to investigate, and may therefore serve as a window to the brain.

Only a limited number of studies has investigated bleeding risk and platelet function in 22q11.2DS, and those who did only included children. Some of these studies indicated impaired platelet function and increased bleeding risk, and one reported a negative correlation between platelet count and age, which may suggest that platelet-associated problems increase with increasing age.
The combination of bleeding risk score and platelet function analysis with platelet transcriptomics and metabolomics may: 1) provide insight into bleeding risk, which is of direct relevance for patient care, and 2) provide insight in mechanisms underlying neurodevelopmental and neuropsychiatric disorders, like schizophrenia, that are frequently seen in 22q11.2DS.

Study objective

- To assess platelet (dys)function in adults with 22q11.2DS and its association with bleeding history.
- To identify alterations in metabolic pathways in 22q11.2DS that may be of relevance to mechanisms underlying neurodevelopmental and neuropsychiatric disorders like schizophrenia.

Study design

The proposed project is a case-control study. We estimate that 12 months are needed for patient inclusion and 8 months for data analysis. We will include 40 adults with 22q11.2DS and 20 healthy controls.
22q11.2DS patients will be included via the outpatient clinic for adults with 22q11.2DS at MUMC+, which takes place once every 2 months and is visited by 3-4 patients a day. In addition to this, 22q11.2DS patients will be recruited via 22q11 patient advocacy organizations or will be contacted by the research team if they have given permission to be contacted for research purposes previously.
Blood drawl at the 22q11 outpatient clinic at MUMC+ is part of routine care for patients with 22q11.2DS; for those visiting this clinic, 6 extra tubes of blood will be collected in addition to the regular blood drawl. For healthy controls, and those patients with 22q11.2DS participating in the study who do not visit the 22q11 outpatient clinic, 7 blood samples will be taken at Maastricht University or a place familiar to the adult with 22q11.2DS.
Healthy control subjects will be recruited via posters at several outpatient clinics such as the ear-nose- throat, ophthalmology and anesthesia outpatient clinics. Healthy subjects will also be recruited through advertising posters at Maastricht University and patient*s family members or supervisors who accompany the 22q11.2DS patient to the outpatient clinic will be informed about the studying can contact the research team to participate.

Study burden and risks

All participants will complete a validated questionnaire; ISTH-BAT.
Administration time of the ISTH-BAT questionnaire is approximately 30 minutes.

In addition, seven tubes of 4-9 mL of blood will be drawn (totally 43 mL of whole blood). This will be done during 1 site visit. Blood drawl may cause local bruising, which usually recovers within a few days. However, for 22q11.2DS adults who visit the outpatient clinic for 22q11.2DS, we will combine the blood drawl with their regular blood drawl for diagnostic purposes. In accordance with treatment guidelines, adults with 22q11.2DS, undergo a venipuncture at least once a year to check various somatic parameters. Participation in this study therefore hardly enhances the burden for adults with 22q11.2DS. For those who are not capable of providing answers on the ISTH-BAT questionnaire due to cognitive impairments, we will ask the substitute decision or caregiver to (help) complete the questionnaire. For healthy volunteers and adults with 22q11.2DS who do not visit the outpatient clinic, the whole study (including informed consent procedure, questionnaire, and blood drawl) will take 1 hour in total.

Group relatedness
The study is group related; it is only possible to extent the knowledge of platelet (dys)function, and the relationship of the metabolome with the presence of schizophrenia, using this group of persons. Given that ~40% of the individuals with 22q11.2DS has an intellectual disability, and only 1:3000 people has a 22q11.2DS in the general population, we would not be able to include enough subjects if we would exclude those mentally incompetent. Therefore, inclusion of mentally incompetent subjects is necessary.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

Vijverdalseweg 1
Maastricht 6226NB
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

Vijverdalseweg 1
Maastricht 6226NB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

- 16 years or older.
- signed informed consent.
Adults with 22q11.2DS
- molecularly confirmed 22q11.2 deletion syndrome.
- Mentally competent (ability to give informed consent) and aged 16 years and older or, in case
the individual is mentally incompetent aged 16 years and older, consent will be given by the legally authorized representative of the subject.

Exclusion criteria

- The presence of any malignancy.
- Use of antiplatelet or anticoagulant drugs within the last two weeks prior to the study.
- Use of anti-inflammatory drugs within the last two weeks prior to the study.
- auto-immune thrombocytopenia
Specific for healthy controls:
- A medical history of thrombocytopenia (<150.000 platelets per mL).
- Increased bleeding risk, defined as a diagnosed bleeding disorder.
- Metabolic disorder.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-09-2021
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	04-06-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 24347
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL75078.068.21
OMON	NL-OMON24347