MicroRNAs as potential biomarkers for noninvasive detection of fetal trisomy 21

Ji Hyae Lim · Da Eun Lee · Shin Young Kim · Hyun Jin Kim · Kyeong Sun Kim · You Jung Han · Min Hyoung Kim · Jun Seek Choi · Moon Young Kim · Hyun Mee Ryu · So Yeon Park

Kaarel Koitne

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Sissejuhatus

Non-Invasive Prenatal Testing

- Trisoomiate tuvastamine:
  - **Downi sündroom - T21**
  - Edwardsi - T18
  - Patau - T13
  - …
- Soo määramine
- ...

MicroRNA-d

- Olulised post-transkriptsioonilised regulaatorid
- 19-25 nt, üheahelalised, mittekodeerivad RNA molekulid
- Inimesel seni tuvastatud ~1900 erinevat
- Transkribeeritakse miRNA geenidelt või muude geenide intronitelt

Miks kasutada?

  - Stabiilsus

NIPT + miRNA-d

Can microRNA profiling in maternal blood identify women at risk for preterm birth?

Michal A. Elovitz, MD; Lauren Anton, PhD; Jamie Bastek, MD, MSCE;
Amy G. Brown, PhD

Circulating MicroRNAs in Maternal Blood as Potential Biomarkers for Fetal Hypoxia In-Utero

Clare L. Whitehead[1]*, Wan Tinn Teh[2], Susan P. Walker[3], Cheryl Leung[4], Luke Larmour[4], Stephen Tong[1]

1 Translational Obstetrics Group, Department of Obstetrics and Gynaecology, Mercy Hospital for Women, Heidelberg, Victoria, Australia, **2** Department of Obstetrics and Gynaecology, University of Melbourne, Royal Hospital for Women, Carlton, Victoria, Australia, **3** Department of Obstetrics and Gynaecology, University of Melbourne, Mercy Hospital for Women, Heidelberg, Victoria, Australia, **4** Department of Obstetrics and Gynaecology, Monash Medical Centre, Clayton, Victoria, Australia

Varasemalt

T21 korral **21. kromosoomi miRNA-de** ekspressioonimustri muutumise analüüs

Töö eesmärgid

1. Leida **kogu genoomist** miRNA-d, mis oleksid potentsiaalseteks biomarkeriteks T21 tuvastamiseks

2. Identifitseerida leitud biomarkerite (miRNA-de) bioloogilised funktsioonid (sihtmärkgeenid)

Töökäik

Valim

Table 1 Clinical characteristics of the study population

Characteristics	Pregnant women carrying trisomy 21fetuses (n=4)	Pregnant women carrying euploid fetuses (n=5)	Non pregnant women (n=2)	P value
At blood sampling				
Age (years)	32.0 (30.0–35.5)	35.0 (32.0–37.0)	29.0 (28.0–30.0)	0.185[a]
Body mass index (kg/m^2)	21.3 (19.3–24.0)	21.0 (20.6–21.4)	21.5 (21.0–22.0)	0.492[a]
Gestational age (weeks)	12.5 (11.9–12.9)	12.5 (11.3–13.0)	–	0.902[b]
Gravidity (n)	2.5 (1.5–4.5)	3.0 (2.0–4.0)		0.905[b]
Nullipara (%)	25	20		0.858
Gender-ratio of fetus (male:female)	2:2	3:2	–	0.764

Values are medians with interquartile range in parentheses

[a] Kruskal-Wallis test

[b] Mann-Whitney U test

Materjal DNA-mikrokiibipõhiseks analüüsiks

	Täisveri	Platsenta
Mitterasedad (2)	✔	
Rasedad (5)	✔	✔
Rasedad T21 lootega (4)	✔	✔

miRNA-de analüüs

- 1349 miRNA-d (1205 inimese, 144 viraalsed)
  - Valiti välja miRNA-d, mille ekspressioon erines täisveres ja platsentas vähemalt 2x
    - Valiti välja miRNA-d, mille ekspressioon erines platsentas T21 ja normaalsete loodete vahel

- T21 tuvastamiseks kasutatavate miRNA-de funktsioonide uurimiseks kasutati miRBase andmebaasi

Tulemused

Leitud miRNA-d

- 299 miRNA-d mille ekspressioon oli vähemalt 2x erinev, võrreldes täisverd ja platsentat
  - 150 üles- ja 149 alla-reguleeritud

- 2 miRNA-d, mille ekspressioon erines T21 loodetega naistel võrreldes normaalsete loodetega naistega

miRNA-d: täisveri *vs* platsenta

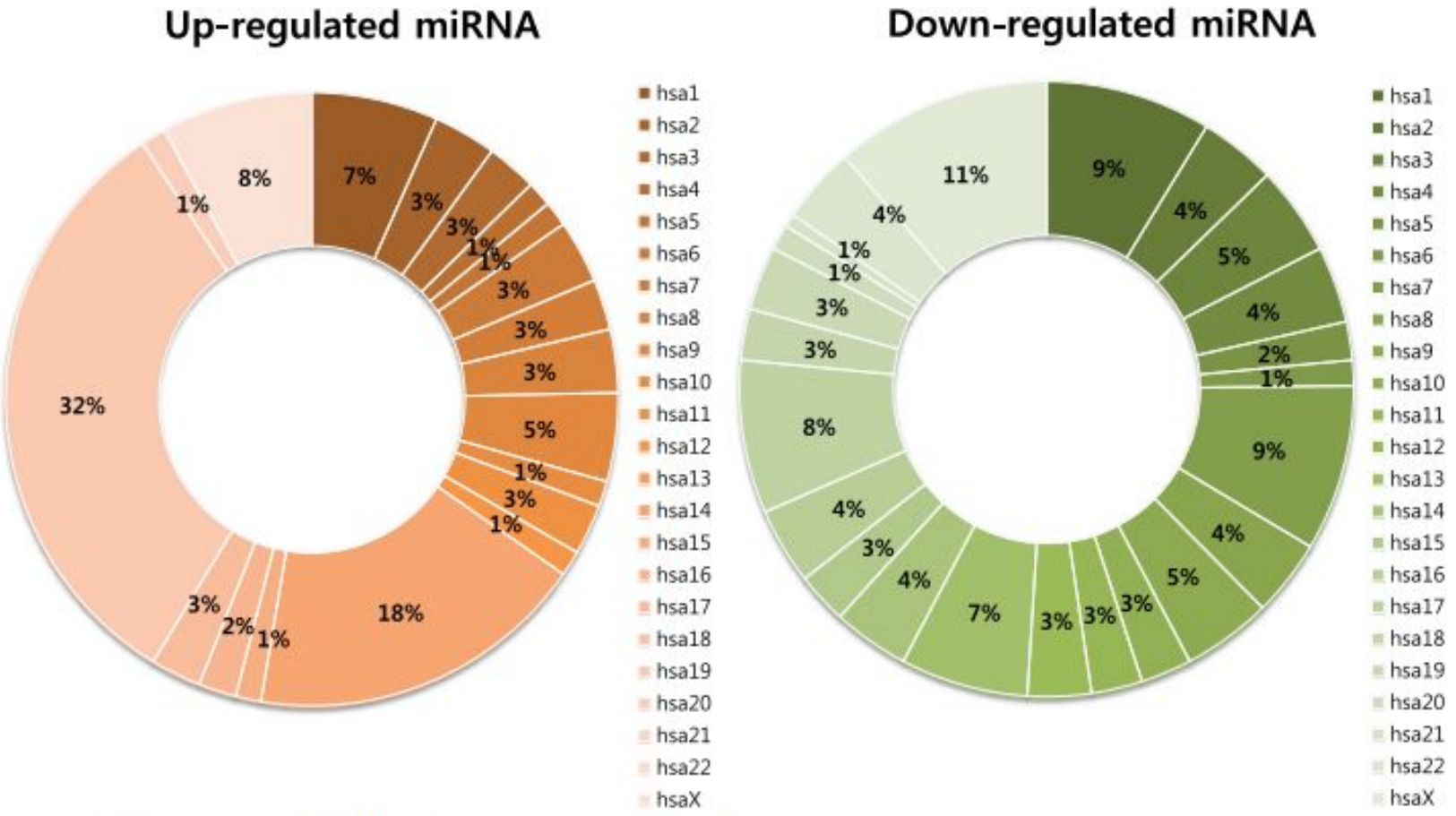

Fig. 1 Chromosomal distribution of miRNAs differentially expressed in placenta

Potentsiaalsed biomarkerid

- **mir-1973** ja **mir-3196**

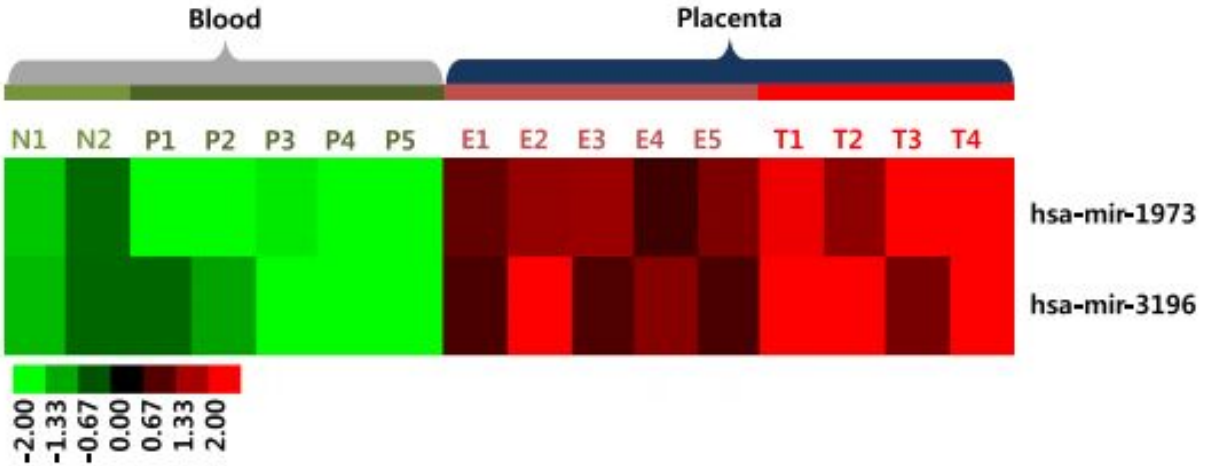

Fig. 2 Expression pattern of miRNA candidates for noninvasive prenatal testing of fetal trisomy 21. miRNAs were clustered using the Pearson uncentered distance metric with average linkage. Each column represents an individual sample and each row represents an individual miRNA. Expression levels of miRNAs are shown in red (up-regulated) and green (down-regulated), with brighter shades indicating higher fold differences. N: non-pregnant, P: pregnant, E: euploid fetus, T: trisomy 21 fetus

Potentsiaalsete biomarkerite märklaudgeenid

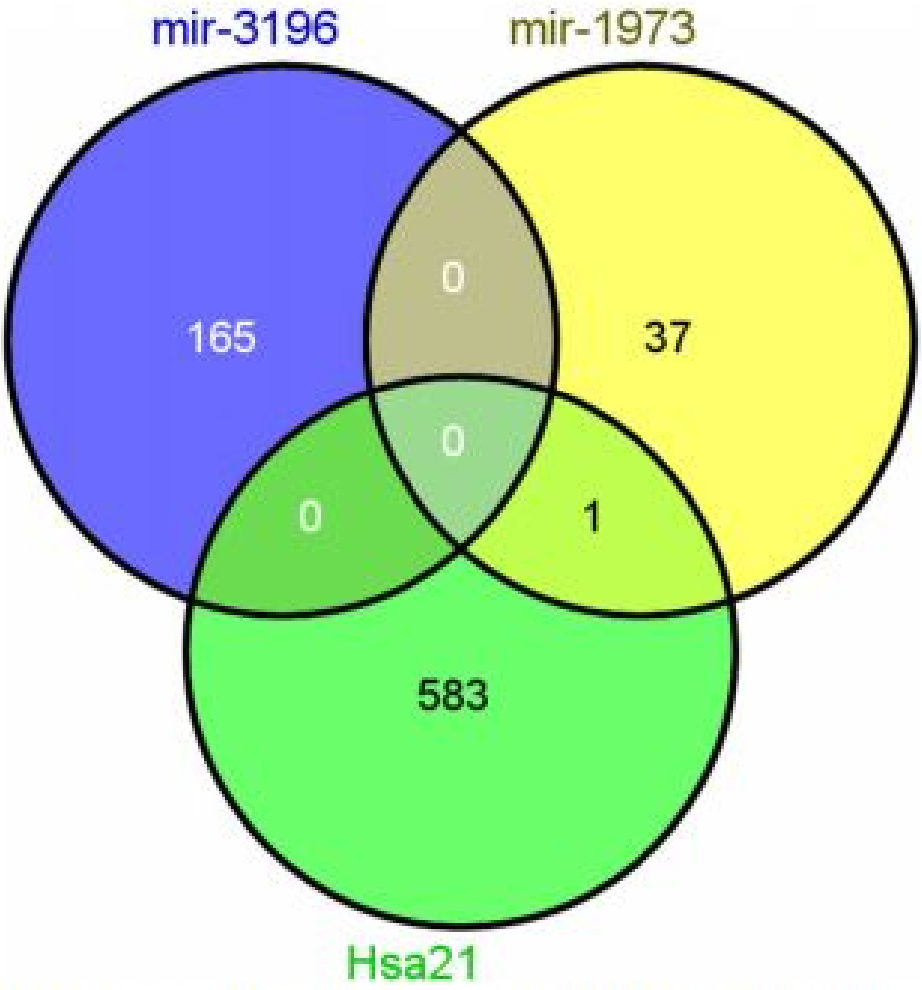

Fig. 3 Hsa21-derived target genes of mir-1973 and mir-3196

Märklaudgeenide seosed haigustega

Table 4 Diseases association with target genes of mir-1973 and mir-3196

Disease	Gene symbol	rawP	adjP
Congenital Abnormalities	*GDAP1, GLI3, ALX4, ADAMTS10, TBX1, BBS5, CYP4F22, COL5A1, SOX3, PAX2, NR5A1, KCNJ15, KAL1, MAFB, HOXD13, DDB1, ZIC1*	9.12E-09	6.38E-08
Mental Disorders	*SYNGAP1, GABRP, PER1, SNCB, VGF, GRIN1, ABCA2, GRIN2D, CPLX1, NALCN, DLGAP3, NEUROD2, NRGN, NEUROG1, SLITRK1*	6.5E-08	2.27E-07
Schizophrenia	*GABRP, TBX1, GRIN1, NRG2, GRIN2D, CPLX1, NALCN, NRGN, MBNL2, SPTBN4, NEUROG1*	1.02E-06	2.38E-06
Syndrome	*GLI3, ALX4, WIPF3, ADAMTS10, TBX1, BBS5, SLC29A3, COL5A1, PAX2, KAL1, MEN1, SLITRK1*	5.60E-05	9.80E-05
Nelson syndrome	*CDK5R2, C2orf16, WIPF3, BBS5, ABCF2, TMEM163, OTX1, BZW2, ZMIZ2, CTNNA2, REPIN1*	3.00E-04	4.00E-04
Nervous System Diseases	*GDAP1, DTNA, SNCB, SOX3, LRRK2, ABCA2, ARC, SLITRK1, ATP1A3, ZIC1*	1.50E-03	1.80E-03
Human immunodeficiency virus	*EIF4G1, IL8, PIK3R2, GRIN1, B3GALT2, MAN1C1, GRIN2D, DDB1, KPNB1, TUBA4A*	2.70E-03	2.70E-03

rawP: p value from hypergeometric test

adjP: p value adjusted by the multiple test adjustment (Benjamini and Hochberg test)

Kokkuvõte

1. Leiti 2 miRNA-d, mille ekspressioon erines T21 ja normaalsete loodete puhul → potentsiaalsed biomarkerid T21 tuvastamiseks
2. **mir-1973** ja **mir-3196** märklaudgeenid on seotud T21-seoseliste haigustega

Tulemuste küsitavus:

- Väike valim

Tänan kuulamast!