



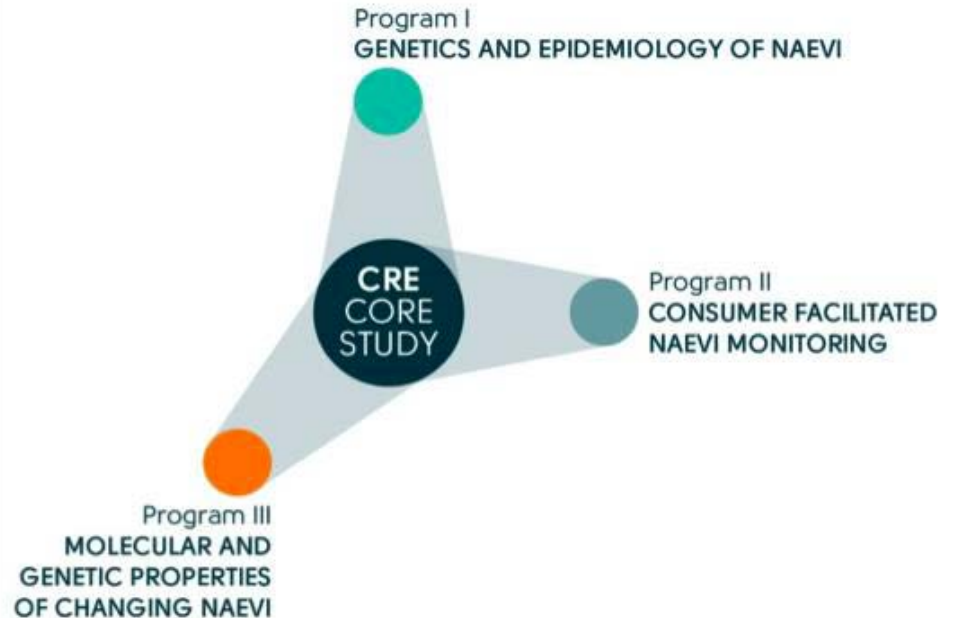
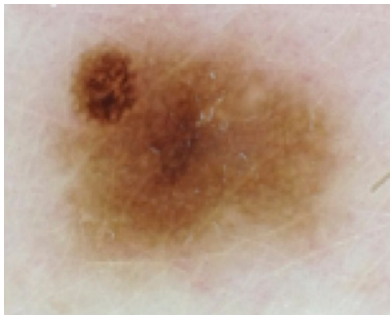
THE UNIVERSITY OF QUEENSLAND

Rick Sturm

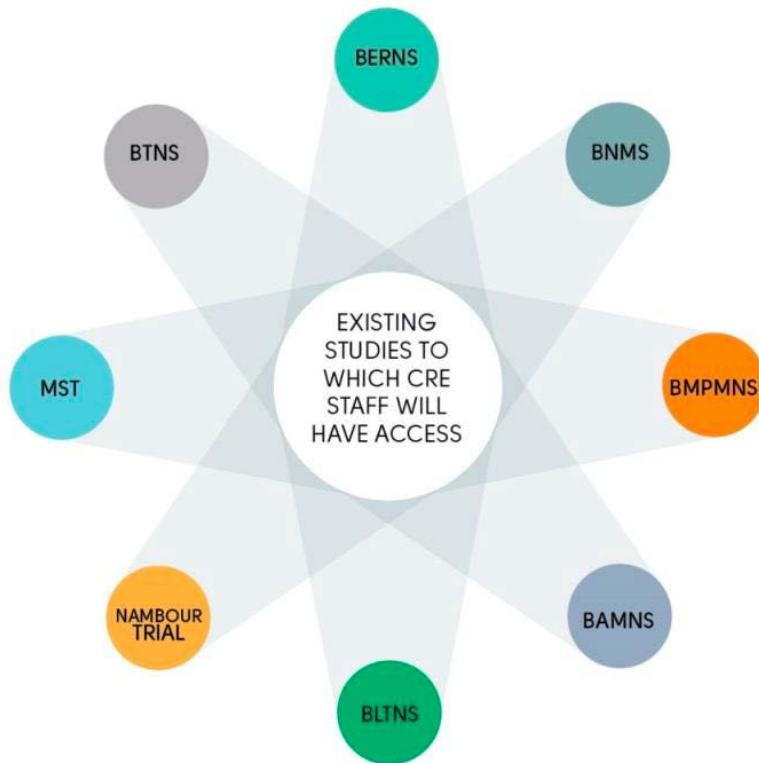
BNMS: Genetic association of naevi morphology and melanoma



twitter.com/uqdrdc



Study Populations available to the CRE



BERNS = Brisbane Electoral Roll Naevus Study, CRE core study n=150

BTNS = Brisbane Twin Naevus Study; n>3,000 (QIMR-B controls 23,724 individuals unaffected by CMM)

BNMS= Brisbane Naevus Morphology Study, n=1,200

BMPMNS = Brisbane Multiple Primary Melanoma Naevus Study, n=100

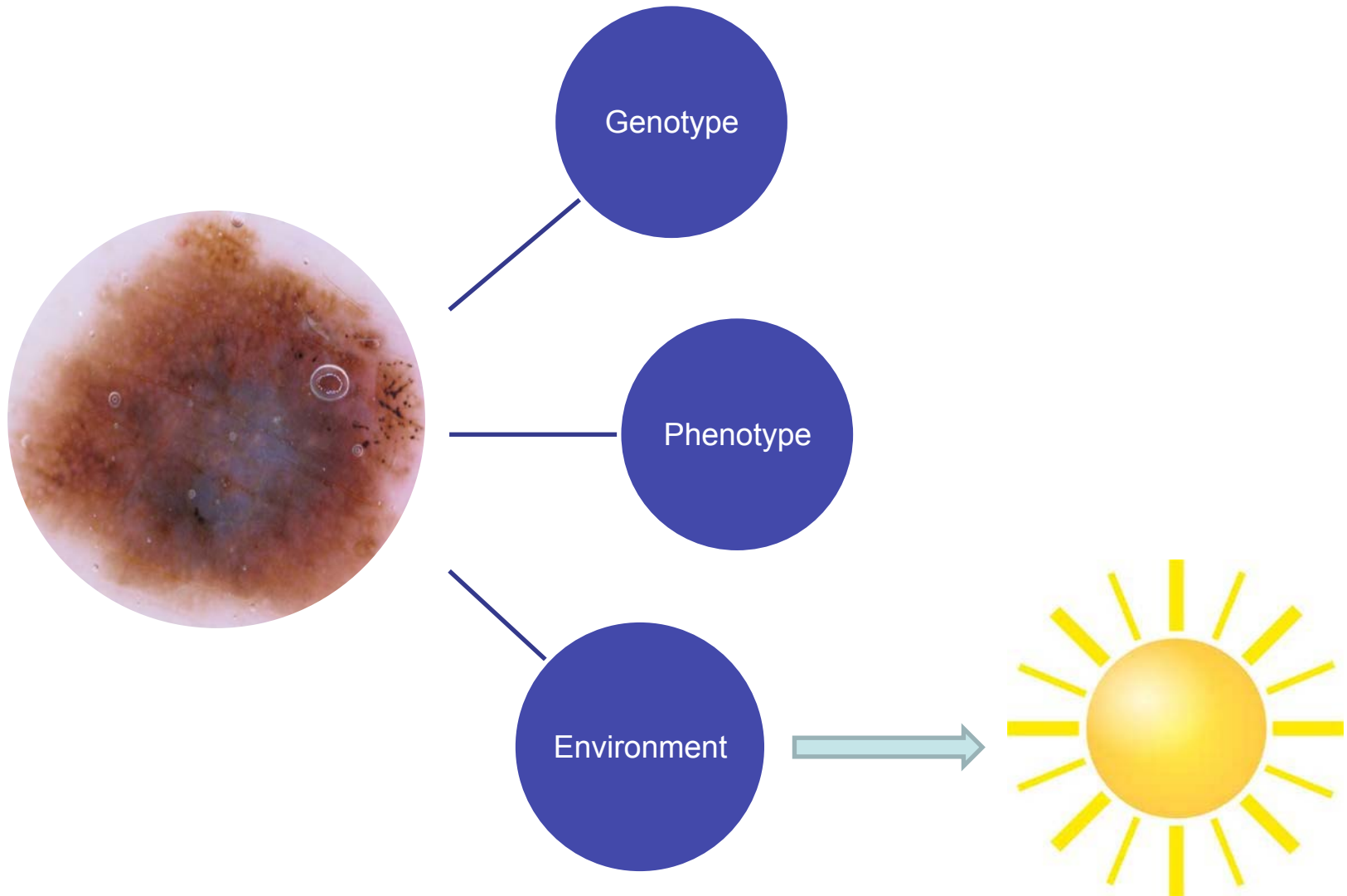
BAMNS = Brisbane Advanced Melanoma Naevus Study n=80

BLTNS = Brisbane Lung Transplant Naevus Study n=90

Nambour trial = Trial of Sunscreen for Melanoma Prevention n= 1,626

MST = QSkin Melanoma Screening Trial n>60,000

What are naevi and how do they arise?



Effect of naevogenesis susceptibility genes and phenotypic correlation with dermoscopic characteristics of naevi

HYPOTHESES:

- **MC1R** variant alleles will have a major influence on innate melanocytic naevus morphology
- Variation in other pigmentation genes such as **TYR**, which are modifiers of melanoma risk, may influence melanocytic naevus colour and morphology
- Genes that have recently been recognised to influence naevus count including **IRF4**, **MTAP** and **PLA2G6** may also influence naevus morphology
- Genes that regulate melanocytic cell function such as **MITF** will also act to modify naevus count and/or morphology

Brisbane Naevus Morphology Study (BNMS) 2011 to 2016

AIM

600 CMM cases or Family History

vs

600 control subjects

N = 1200

Interim analysis of survey at 3 years

240 CMM cases + 76 Family History

256 control subjects



Total Dec 2013 with phenotype + genotype N = 572

Recruited as of April 2016 N > 1100

Naevi classified by size, profile, colour and dermoscopic naevus pattern

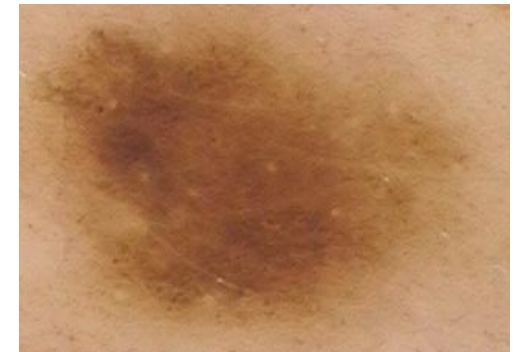
13,587 melanocytic naevi
>5mm



Globular
15.6%

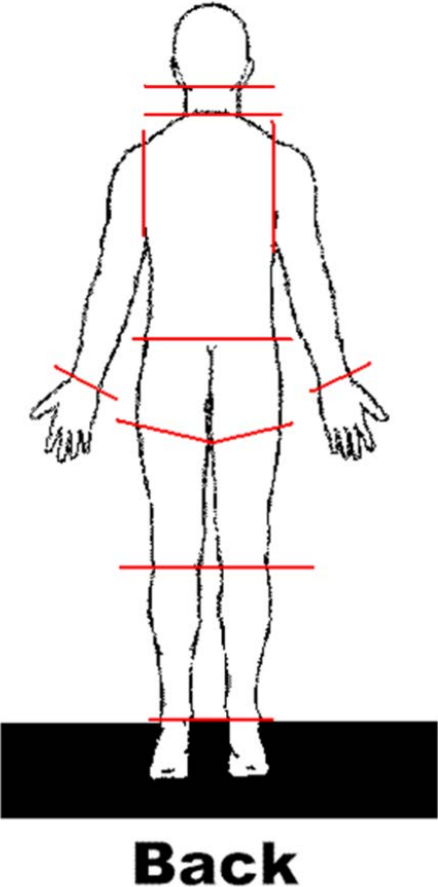
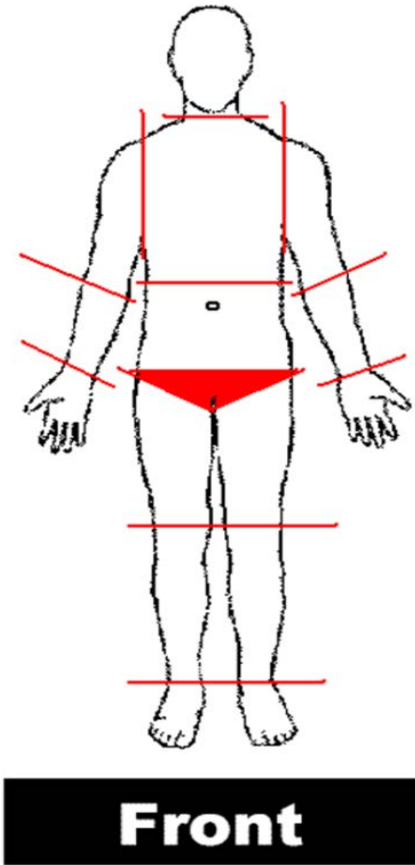


Reticular
21.9%

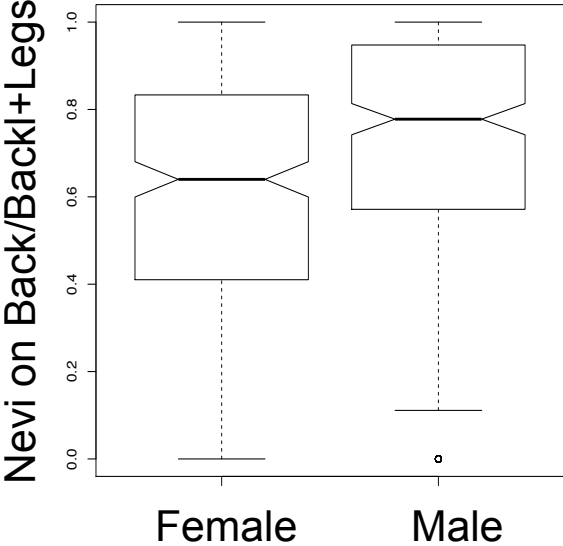


**Homogeneous/
Nonspecific**
62.5%

Total body naevus count by body-site and sex



Female vs Male





Collection of saliva for genetic analysis

Assess pigmentation using Spectrophotometer

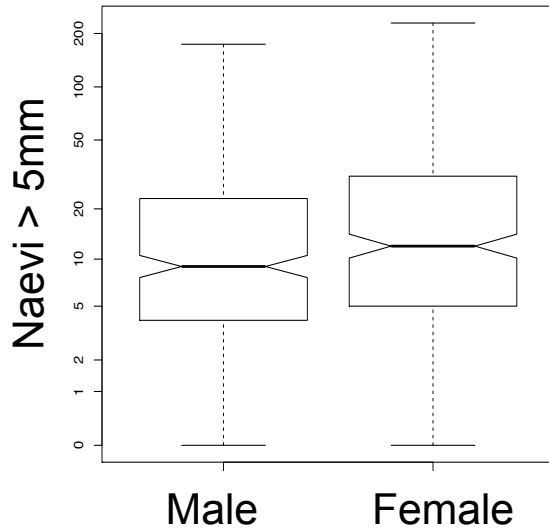
Assess freckling density on face, hand & shoulders

Documentation of patient demographics, sun exposure background, personal and family skin cancer / naevi history, medications

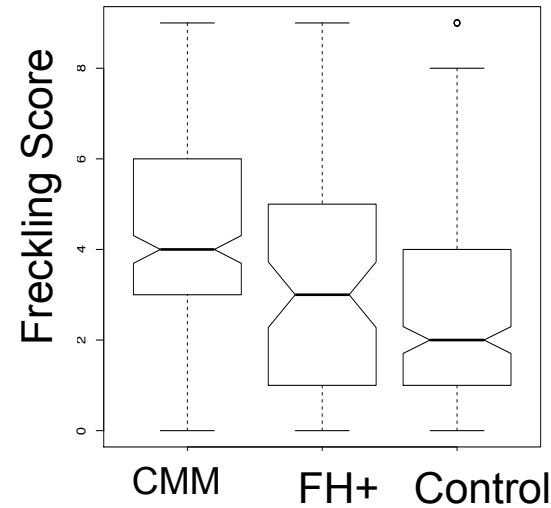
Photographic documentation of eye colour

Phenotypic Characteristics of BNMS

Naevus count vs Sex

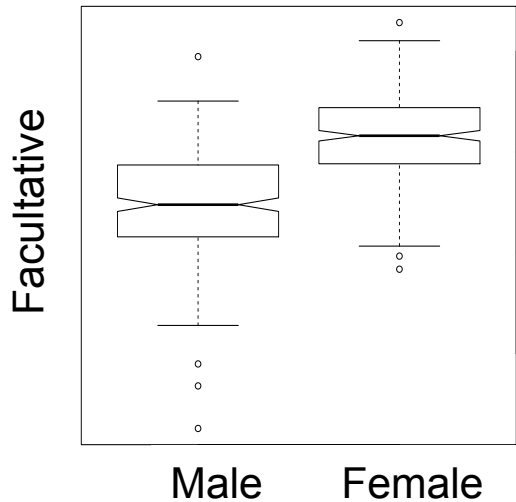


Freckling score vs Melanoma

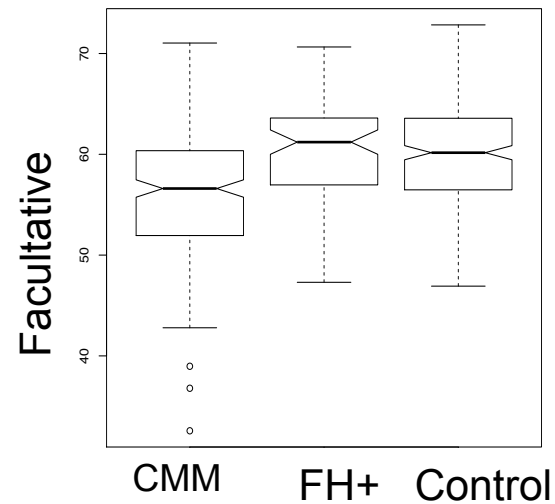


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Skin Reflectance vs Sex

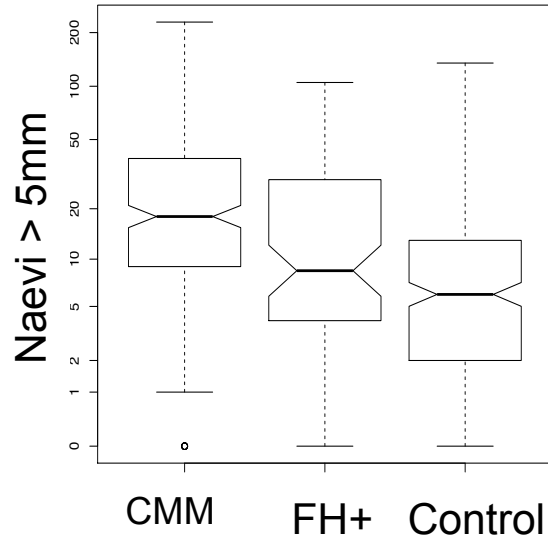


Skin Reflectance vs Melanoma

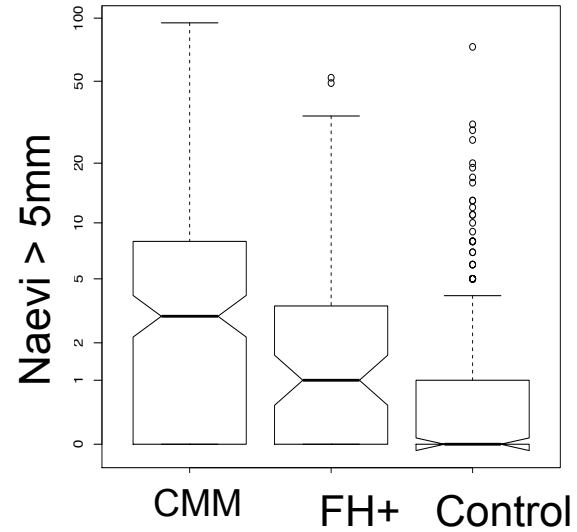


Naevus Count vs Melanoma

Total

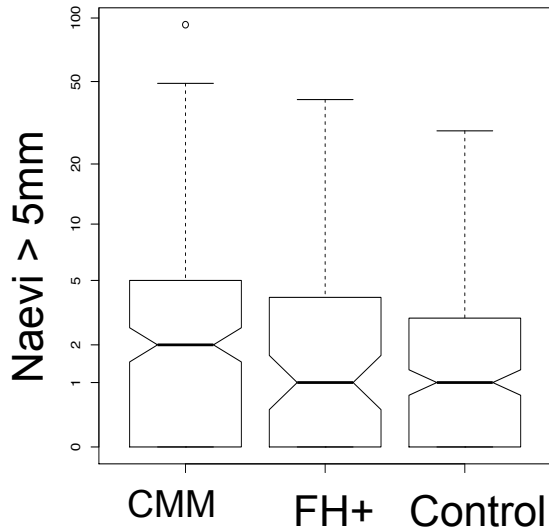


Reticular

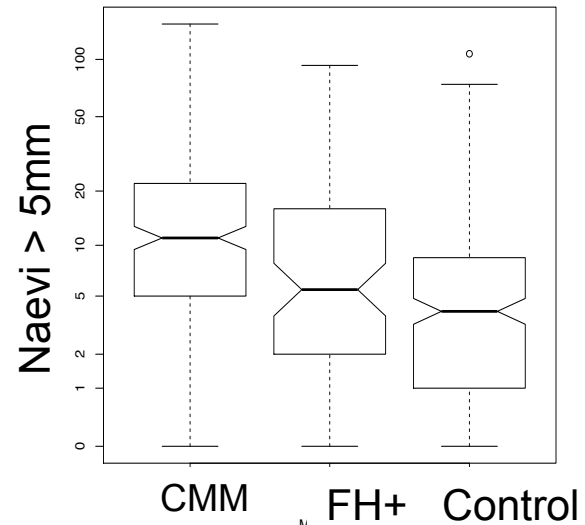


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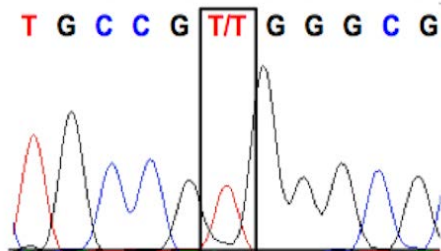
Globular



Nonspecific



Sanger Sequencing MC1R Genotyping



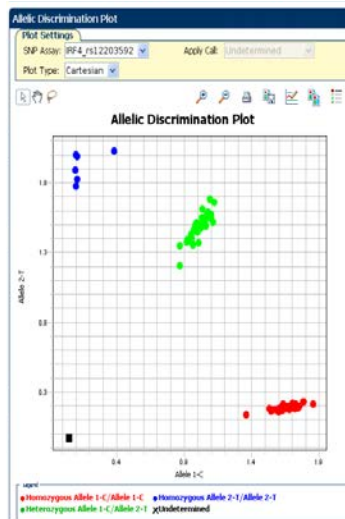
Whole Exome Sequencing (WES)

MC1R R160W +/-
chr16:89986144 C>T



Genotyping platforms

Sequenom and Taqman based SNP Genotyping



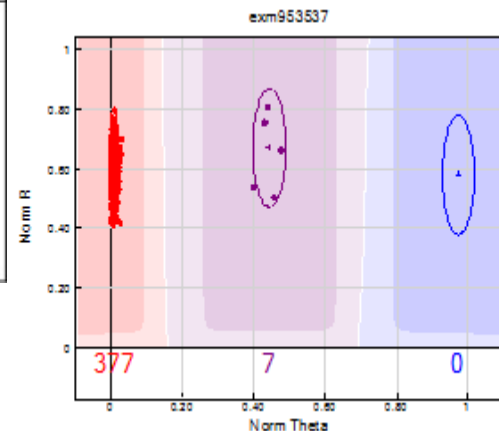
Illumina CoreExome 500,000 SNPs

Figure 1: HumanCoreExome-24 BeadChip



The HumanCoreExome-24 BeadChip enables informative genotyping of tag SNP and exome-focused markers across diverse world populations, delivering high-quality data that can be used in various downstream applications.

Gen	rs	Chr	Nucleotide Change		Protein Change
SLC45A2	rs16891982	5	c.1122 G>C	TTC>TTG	p.Phe374Leu
HERC2	rs12913832	15	c.13272+874T>C	-	-
SLC24A5	rs1426654	15	c.331A>G	ACA>GAC	p.Thr111Ala
IRF4	rs12203592	6	c.492+386 C>T	-	-
OPN/SPP1	rs11730582	4	g.88896421T>C	-	-
OGG1	rs1052133	3	c.977C>G	TCC>TGC	p.Ser326Cys
GSTP1	rs1695	11	c.313A>G	ATC>GTC	p.Ile105Val
MITF	rs149617956	3	c.952G>A	GAA>AAA	p.Glu318Lys
TYR	rs1042602	11	c.575C>A	TCT>TAT	p.Ser192Tyr
TYR	rs1126809	11	c.1205G>A	CGA>CAA	p.Arg402Gln



Candidate genes and SNPs associated with CMM in BNMS

Rs/loc	chr	ps	p-value	-log10(p)	gene name
rs11570734	22	38.518622	0.0003	3.541	PLA2G6
mc1r	16	21.800000	0.0006	3.222	R,r,w
rs4820314	22	38.518538	0.0007	3.175	PLA2G6
rs7023954	9	21.816758	0.0018	2.743	MTAP V56I
mc1r_R163Q	16	89.986154	0.0036	2.449	MC1R R163Q
rs7023329	9	21.816528	0.0048	2.319	MTAP

CDKN2A carriers identified by Whole Exome Sequence (WES) Analysis

Arch Dermatol Res
DOI 10.1007/s00403-015-1582-y

CONCISE COMMUNICATION

High incidence of primary melanomas in an *MC1R* RHC homozygote/*CDKN2A* mutant genotype patient

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