2015
대 한 모 발 학 회
제14차 Hair Forum

- 일시: 2015년 8월 22일(토) 15:30-18:35
- 장소: 대전 호텔리베라 유성

대 한 모 발 학 회

2015
대한모발학회 제14차 Hair Forum

2015. 8. 22(토) **호텔리베라 유성**

일 정 표

오후

3:30–3:40 개회사 ····· 회 장 심우영

일정소개 ····· 총무이사 강 훈

진행 ····· 학술이사 권오상

제1부: 자유연제 발표 5분, 질의응답 5분

3:40–3:50 **Experience of combination therapy with finasteride and low dose dutasteride in the treatment of male pattern hair loss**
····· 서남의대 이숙영, 손현옥, 전신욱, 김종백, 노병인 / 6

3:50-4:00 **Proposal for genetic study in alopecia areata**
····· 충남의대 이 영 / 10

4:00-4:10 **The association between exercise and hair loss: Does exercise cause hair loss?**
····· 연세대 원주의대 최재웅, 전명수, 이원수 / 20

4:10-4:20 **Hair growth stimulated by conditioned media of umbilical cord blood-derived mesenchymal stem cells is enhanced by priming with growth factor.**
····· 중앙의대 김순례 / 23

4:20-4:30 **Premature hair graying treated with ferrous sulfate**
····· 경희의대 최중윤, 서동우, 유박린, 심우영 / 31

4:30-4:40 **중증원형탈모증 환자에서 가발착용의 효과 및 비용지출**
····· 전북의대 박 진 / 36

4:40-4:50 **Pros and cons of the scalp medical tattoo**
..... 연세모벨르피부과 **박진모** / 41

4:50-5:10 **Coffee Break**

제2부: 주제 발표 [백모]

5:15-5:40 **Hair graying: Clinical features & significance**
..... 서울의대 **조성진** / 44

5:45-6:10 **Hair pigmentation: Basic biological aspects of follicular melanocyte**
..... 연세의대 **김도영** / 60

6:15-6:25 폐 회 사 ..... 회 장 **심우영**

6:25-6:35 기념촬영

6:35- 저녁식사

2015

대한모발학회

제14차 Hair Forum

제 1 부 : 자유연제 발표

The Korean Hair Research Society

Experience of combination therapy with finasteride and low dose dutasteride in the treatment of male pattern hair loss

Suk Young Lee, Hyun Ok Son, Sin Wook Chun, Jong Baik Kim, Byung In Ro

Department of Dermatology, Myongji Hospital, Seonam University College of Medicine
Goyang-si, Gyeonggi-do, Korea

Experience of Combination Therapy with Finasteride and Low Dose Dutasteride in the Treatment of Male Pattern Hair Loss

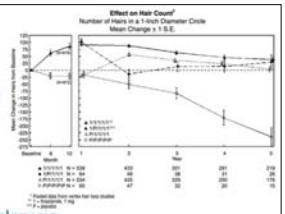
Suk Young Lee, Hyun Ok Son, Sin Wook Chun, Jong Baik Kim, Byung In Ro

Department of Dermatology, Myongji Hospital, Seonam University College of Medicine Goyang-si, Gyeonggi-do, Korea

Introduction

- The pathogenesis of Androgenetic alopecia is still unclear
  - Testosterone convert to Dihydrotestosterone(DHT) by 5α-reductase(5AR)
    - Miniaturization of hair follicle
- 5α-reductase(5AR)
  - A major enzyme in the pathophysiology of AGA
  - Type I : Sebaceous and sweat gland
  - Type II : Genital skin, beard and scalp hair follicles
  - Type III : Ubiquitously throughout the dermis and epidermis

- 5α-reductase inhibitor
  - Finasteride (Type II)
  - Dutasteride (Type I and II)



- Treatment for androgenetic alopecia
  - 1mg of Finasteride daily
    - Maximal hair regrowth is seen within 2 years and declines slightly thereafter

Eur J Dermatol. 2002;12:38-49

- Men who responded initially to finasteride, later notice a resumption of hair loss → May need additional treatment

Dermatology

Australasian Journal of Dermatology (2013) 54, 48–51 doi: 10.1111/j.1440-0960.2012.00000.x

BRIEF REPORT

Combination therapy with finasteride and low-dose dutasteride in the treatment of androgenetic alopecia

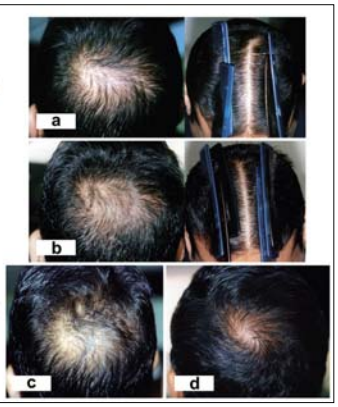
Ann Boyapati and Rodney Sinclair

Department of Dermatology, St Vincent's Hospital Melbourne, Victoria, Australia

Case report(M/47)

- A 2-year history of hair loss
- 1mg of oral Finasteride daily
  - 6 months later : good response
  - Maximum hair growth effects : 2 years
  - Next 4 years : his response had begun to decline and a reduction in his hair density was noted
- Add Dutasteride, 0.5mg/week
  - Within 3 months : a dramatic increase in his hair density
- Rationale : Not known

- (a) baseline pretreatment
- (b) good response after 6 months of finasteride therapy
- (c) reduction in hair density after 4 years of continuous finasteride therapy
- (d) hair regrowth after addition of low-dose dutasteride(0.5mg/week) to finasteride therapy

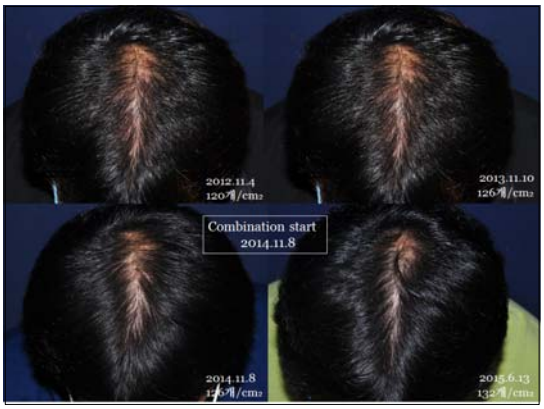


In Our Cases

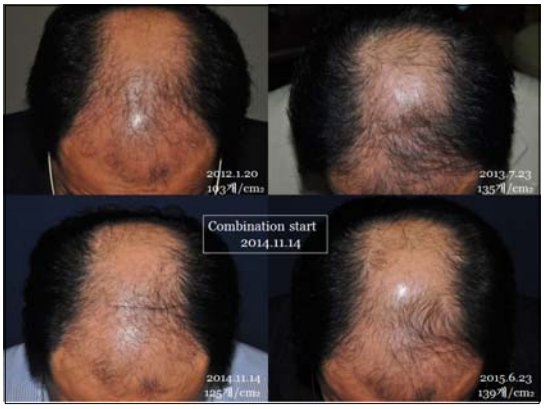
- 4 Patients
  - Who visited Alopecia Clinic, Department of Dermatology, Myongji Hospital, Seonam Univ. College of Medicine, 2014.11-12
  - Add Dutasteride 0.5mg /week while finasteride 1mg daily was continued
  - Baseline and 6 months follow up phototrichogram were taken

Sex/Age	N-H type	Propecia Hx.	Combination start
M/40	MPHL II	24 months	2014.11.8
M/52	MPHL IV	34 months	2014.11.14
M/60	MPHL IV	44 months	2014.12.19
F/58	FPHL III	24 months	2014.12.23

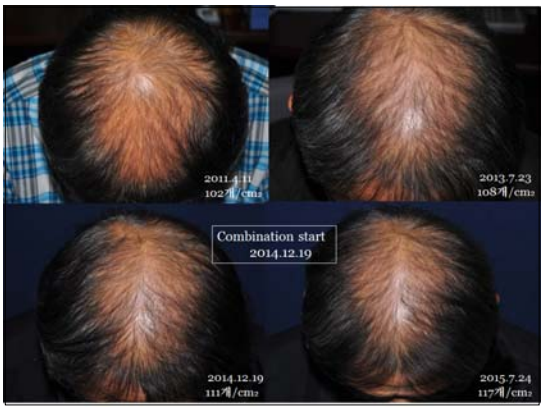
M/40(MPHL II)



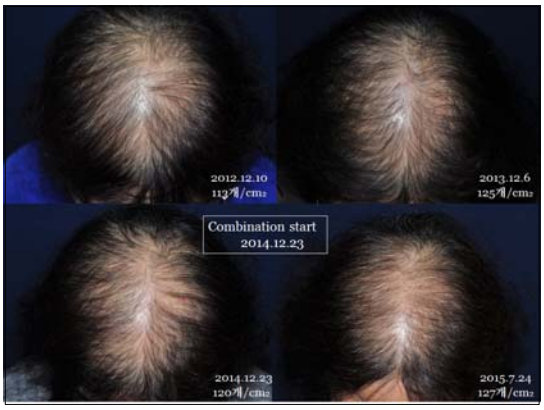
M/52(MPHL VI)



M/60(MPHL VI)



F/58(MPHL III)



DISCUSSION

Discussion

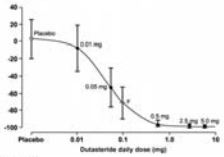
- Finasteride
  - Type II 5α-reductase inhibitor
  - Also a potent inhibitor of type III 5α-reductase

Azzouni F et al. Adv. Urol. 2012

- Dutasteride
  - Dual (type I and II) 5α-reductase inhibitor
- Dihydrotestosterone(DHT)
  - Intraprostatic DHT : 99% ↓ with dutasteride
  - Scalp DHT : 51% ↓ with dutasteride and 41% ↓ with finasteride
    - A triple 5α-reductase inhibitor could be useful in AGA

- Combination therapy
  - Finasteride and low-dose dutasteride
- Continuing Finasteride
  - It worked initially – provide a good blockage of type II
  - Also a potent inhibitor of type III 5AR
- Low-dose Dutasteride
  - Additional blockade of type I 5AR rather than the enhancement of the type II or III 5AR

- Dutasteride 0.5mg/week
  - Long pharmacological and biological half-life
  - Terminal elimination half-life of 5 weeks



- No significant side effects were seen

Discussion

- Functional role in the skin of type III 5AR has not yet been elucidated
- Further large and multicenter studies are needed

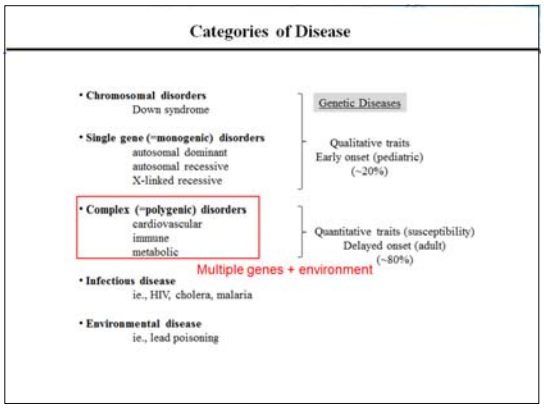
Conclusion

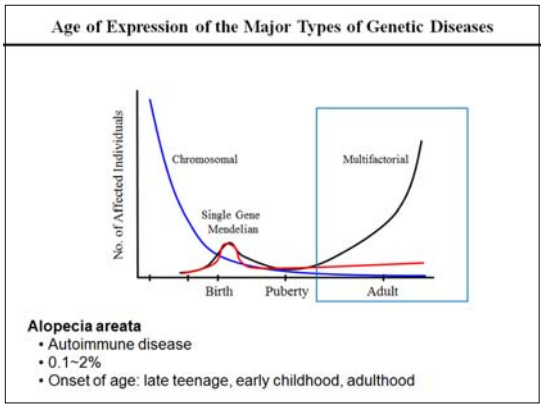
- Enhanced efficacy due to a triple blockage of the 5AR leading to lower scalp DHT concentrations
- Some patients with AGA who have poor response to long term use of finasteride, addition of low-dose dutasteride to their ongoing finasteride treatment could be an option

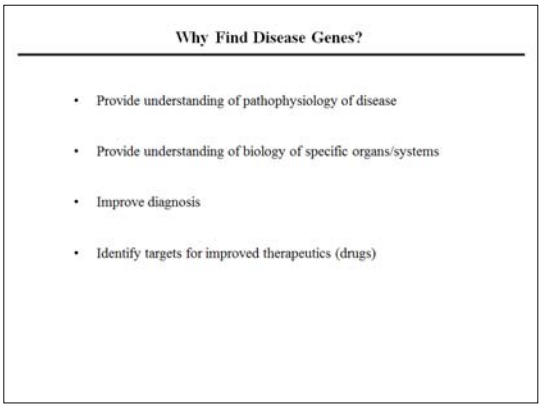
Proposal for genetic study in alopecia areata

Young Lee

Department of Dermatology, College of Medicine
Chungnam National University, Daejeon, Korea

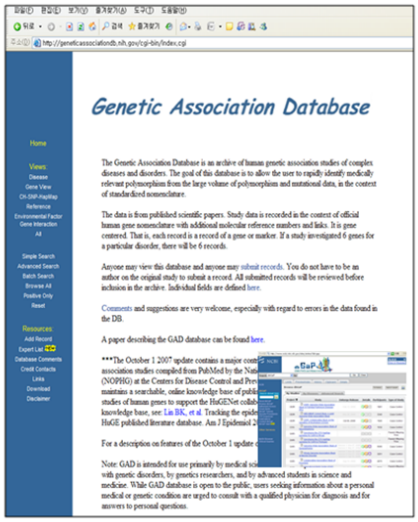






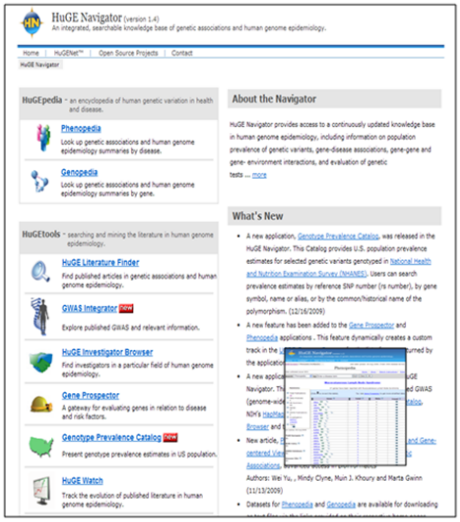
Search Engine for GWAS Data

Genetic Association Database



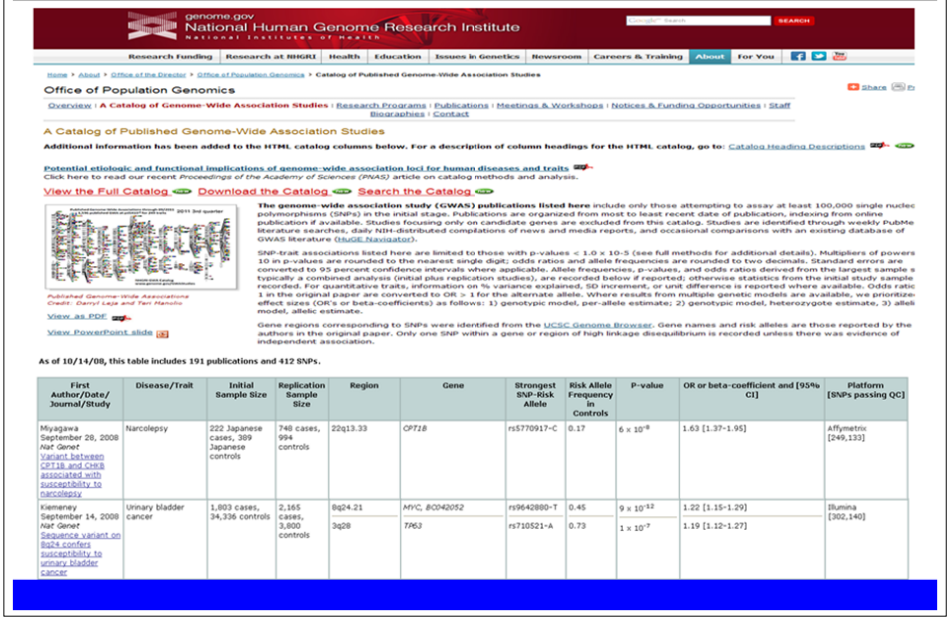
http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap

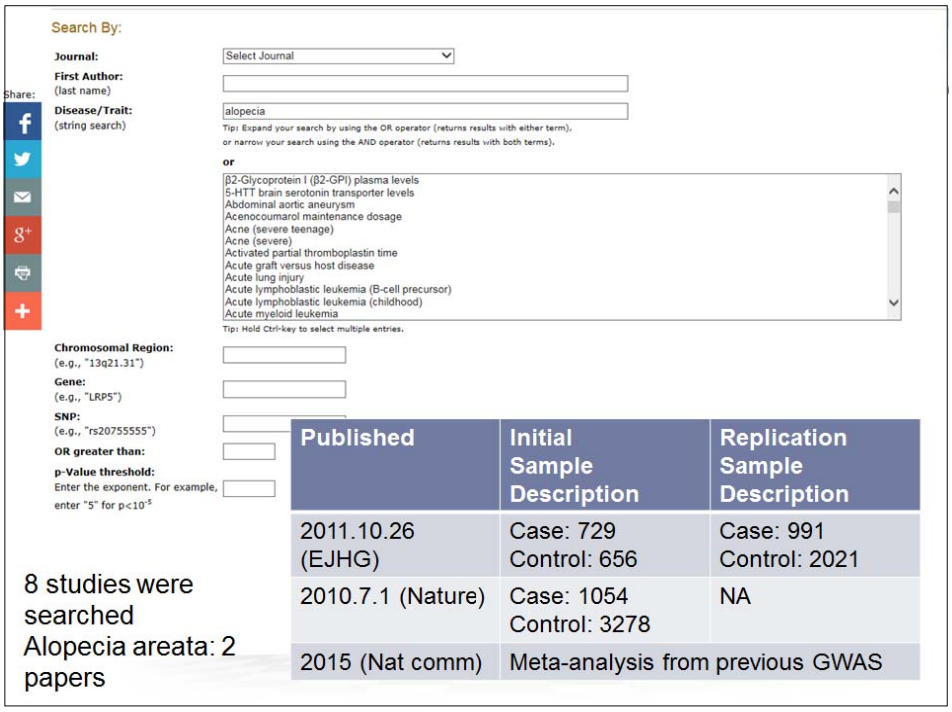
HuGE Navigator



http://www.hugenavigator.net/

NHGRI Catalog of GWA Studies: http://www.genome.gov/gwastudies/





동아시아인의 제2형 당뇨병에 대한 전장 메타분석

Meta-analysis of genome-wide association study for type 2 diabetes in East Asians

질병관리본부 국립보건연구원 유전체센터 형질연구과
고민진

지난 5년에 걸쳐 다양한 복합질환과 여러 형질에 대하여 전장유전체 연관분석 및 메타분석에 대한 결과들이 세계 주요저널에 집중적으로 보고되고 있다. *대부분의 분석은 서구 유럽인을 대상으로 이루어져 왔으며*, 최근 일본인을 대상으로 한 제2형 당뇨병의 전장유전체 연관분석 결과가 일부 보고되고 있으나, 비 유럽인을 대상한 연구는 아주 미미한 실정이다. …..… 중략 이에 대해 동아시아인에서 검증연구를 실시한 결과 26개 유전변이(CDKN2A/B, KCNQ1 등)가 당뇨병 발생과 연관성이 있는 것($p<0.05$)으로 확인되었다. *서양인에서는 유의한 양상을 보였지만, 아시아인에서는 유의하지 않은 결과를 보인 경우에는 대립인자의 빈도차이를 통해 아시아인의 당뇨병 발생에 미치는 영향은 유럽인과는 다르게 나타날 수 있다는 것을 확인하였다.*

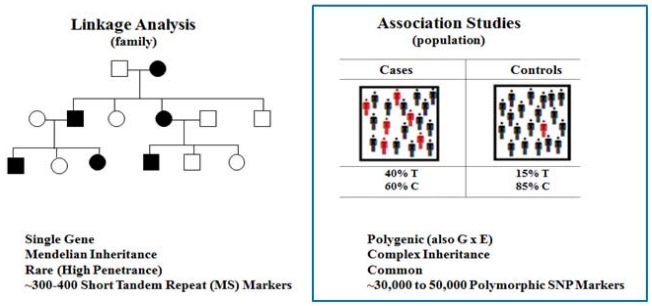
http://www.nih.go.kr/NIH_NEW/main.jsp

- **골다공증성 골절 및 골 강도에 대한 전장유전체 연관성 연구**
  아산/가톨릭병원으로부터 1,626명 및 일본 이화학연구소로부터 929명에 대해 검증 분석을 수행
- **유방암 전장유전체연관분석 연구**
  한국인 유방암 환자 시료 2386명을 서울유방암연구회로부터 확보하여 고밀도 SNP칩을 이용한 유전형질 확보. case-control genome wide association 연구를 위한 대조군으로 한국인유전체역학사업의 일부인 대도시 코호트 여성 2387명의 SNP칩 데이터를 이용하여 질환과의 연관 분석을 수행
- **위암 전장유전체연관분석 연구**
  한국인 위암 환자 2,034명을 서울 삼성의료원으로부터, 대조군으로 이용할 시료 4,302명을 대도시 코호트로부터 확보하고 고밀도 SNP chip을 사용하여 장(intestinal type), 미만형(diffuse type) 위암과 연관성 분석 수행. 국립암센터의 위암시료 1,055 개와 유전체 센터의 안성 및 안산 코호트 3,507개를 이용하여 2차 검증분석을 수행
- **관상동맥 전장유전체연관분석 연구**
  한국인에서 관상동맥 질환의 시료 2,293개를 서울대학병원, 연세대학 병원, 삼성의료원, 유전체센터의 4개 기관으로 구성된 GenRIC Working Group으로부터 확보. 유전체센터의 대도시 코호트로부터 정상인 4,302개를 확보하여 1차 전장유전체 연관분석을 수행. 1차 분석에서 의미 있게 나온 유전변이들을 동양인의 독립된 인구집단에서 확인하기 위해 검증연구를 수행(일본의 나고야의 코호트인 KItanagoya Genome (KING) study로부터 관상동맥 질환 시료 3,052개와 정상인 시료 4,976개를 이용)

Genetic analysis in multifactorial disease

- **Genetic analysis methods**
  - Linkage analysis
  - Association study
- **Study population**
  - Reduce the heterogeneity

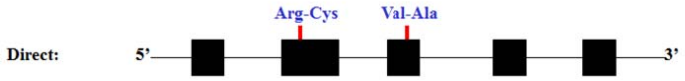
Strategies for Disease Gene Identification



* Linkage vs. Association Studies:
- Evidence of mono/oligogenic disorders or major gene involvement --→ Linkage is the choice,
- Otherwise, association study (especially, gene x environment study)

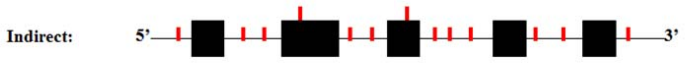
요인	단일유전자 질병 (monogenic disease)	다유전자 (복합) 질병 (polygenic/complex disease)
유전자빈도	매우 낮음 (희귀)	높음 (>1%)
전달정도	높음	낮음
절대적/상대적위험도	높음	낮음
집단내 위험도	낮음	높음
연구재료	가계	집단
연구방법	유전연관분석 (linkage analysis)	연관성연구 association study
사용기술	STR genotyping Exome sequencing	SNP chip

SNP Selection for Association Studies



Catalog and test all coding SNPs for function: ➔ **Candidate Gene Approach**

기능적으로 중요한 유전변이형을 선별하여 연관성 분석 (rSNP, cSNP)

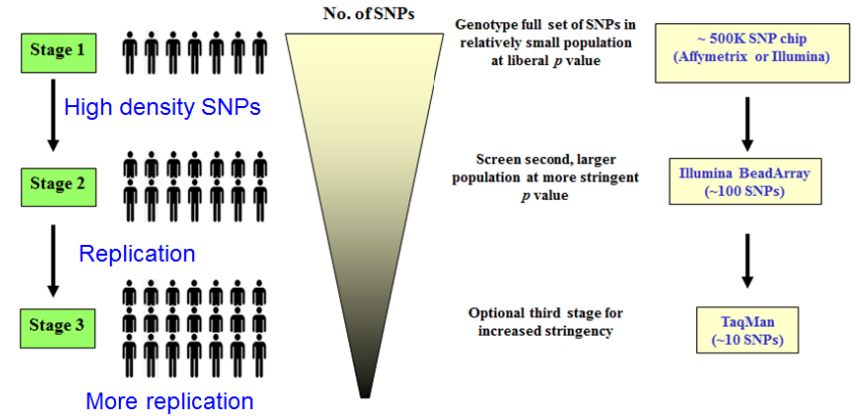


Use dense map of SNPs and test for LD (use association to find sites in entire sequence with function): ➔ **Genome-wide Association Approach**

전체유전체, 특정유전체 영역에 일정한 간격을 두고 유전변이형 마커를 선별하여 질병 연관성 연구를 수행

Ref: Collins, Guyer, Chakravarti. *Science* 278:1580-81, 1997.

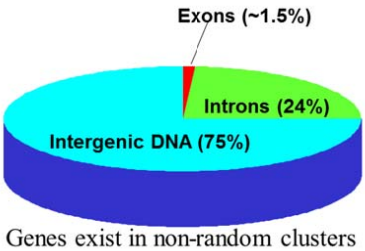
Multi-Stage Approach: to Minimize Sample Sizes & to Overcome Multiple Testing Problem



대용량 SNP chip → random error

Ref: Hirschhorn JN and Daly MJ. 2005. Nature Reviews Genetics 6: 95-108, 2005

Distribution of DNA According to Functional Location



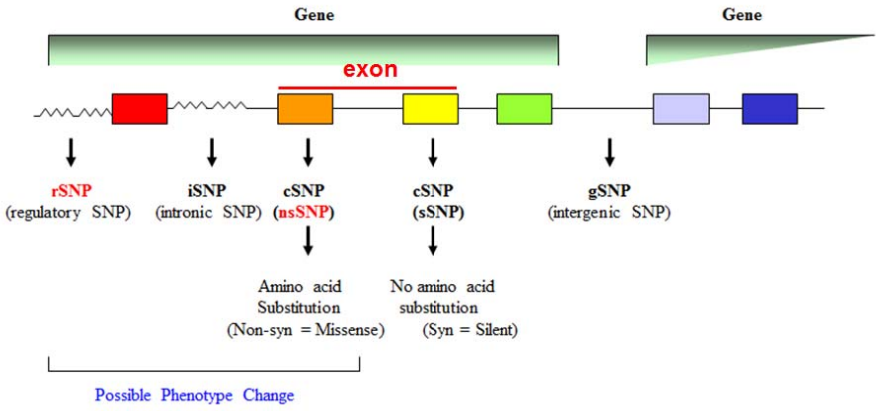
Genes exist in non-random clusters

An overview of natural genetic variation from the literature and in **510 human candidate genes** resequenced for variation discovery.

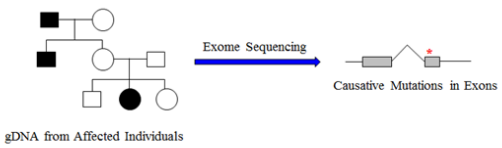
The average human gene: **126 SNPs per gene**
46 common SNPs (≥ 5% MAF)
5 cSNPs

Crawford DC et al. Annu Rev Genomics Hum Genet 2005;6:287-312

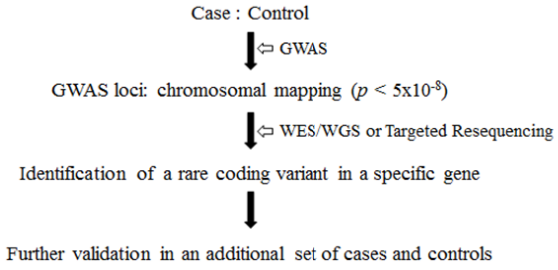
Classification of SNP by Location



- GWAS: 80% of the SNPs on the array are intron or intergenic
- Exome:
  - All exons in the human genome
  - Most functionally relevant ~1.5% of the genome (180,000 exons, 21,000-23,000 protein coding genes) in human genome where the majority of known disease-causing mutations reside
- 85% of the disease-causing mutations are estimated to be located at protein-coding region
- Exome sequencing enables the discovery of both and rare functional genomic variations/mutations underlying Medelian and complex genetic disease



How To Study Rare Variants in common Diseases/Traits: (1) Combining GWAS, WES/WGS and Imputation in a Case-Control Population to identify causal rare variants



Step 1. Study Design

- Select target disease: Heritability
- Case-control criteria: Target phenotype(s)
- Determine # of samples (=Power)

Requirements for complex diseases: high density marker sets, larger sample size (> 1,000~10,000)

- Number of SNPs: candidate gene, pathway, genome
- Others:
  - Ethnicity
  - Replication
  - Cost & DNA requirements

How Can We Reduce (Phenotypic) Heterogeneity ?

- Define the trait consistently and accurately
  표현형 (질병)을 정확하고 일관된 기준으로 정한다
- Identify subtypes:
  - Early onset - 조기발병군 (Early onset)
  - Severe expression - 심한표현형 (severe expression)
  -Atypical expression - 특이한 표현형 (atypical expression)
- Use strict and narrow population definitions
  가능한 좁고 엄격한 질병 집단을 정한다
- Alopecia universalis / alopecia totalis
- Early onset (< 10yr)
- Familial cases, large number of patients

OPEN ACCESS Freely available online

PLOS ONE

Exomic Sequencing of Immune-Related Genes Reveals Novel Candidate Variants Associated with Alopecia Universalis

Seungbok Lee[1,2☯], Seung Hwan Paik[3☯], Hyun-Jin Kim[1,2], Hyeong Ho Ryu[3], Soeun Cha[1], Seong Jin Jo[3], Hee Chul Eun[3,4,5], Jeong-Sun Seo[1,2,6,7,8], Jong-Il Kim[1,2,6,7*], Oh Sang Kwon[3,4,5*]

1 Genomic Medicine Institute (GMI), Medical Research Center, Seoul National University, Seoul, Korea, **2** Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Korea, **3** Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea, **4** Laboratory of Cutaneous Aging and Hair Research, Clinical Research Institute, Seoul National University Hospital, Seoul, Korea, **5** Institute of Dermatological Science, Seoul National University College of Medicine, Seoul, Korea, **6** Department of Biochemistry and Molecular Biology, Seoul National University College of Medicine, Seoul, Korea, **7** Psoma Therapeutics Inc., Seoul, Korea, **8** Macrogen Inc., Seoul, Korea

Abstract

Alopecia areata (AA) is a common autoimmune disorder mostly presented as round patches of hair loss and subclassified into alopecia totalis/alopecia universalis (AT/AU) based on the area of alopecia. Although AA is relatively common, only 5% of AA patients progress to AT/AU, which affect the whole scalp and whole body respectively. To determine genetic determinants of this orphan disease, we undertook whole-exome sequencing of 6 samples from AU patients, and 26 variants in immune-related genes were selected as candidates. When an additional 14 AU samples were genotyped for these candidates, 6 of them remained at the level of significance in comparison with 155 Asian controls ($p<1.92\times10^{-3}$). Linkage disequilibrium was observed between some of the most significant SNPs, including rs41559420 of *HLA-DRB5* ($p<0.001$, OR 44.57) and rs28362679 of *BTNL2* ($p<0.001$, OR 30.21). While *BTNL2* was reported as a general susceptibility gene of AA previously, *HLA-DRB5* has not been implicated in AA. In addition, we found several genetic variants in novel genes (*HLA-DMB*, *TLR1*, and *PMS2*) and discovered an additional locus on *HLA-A*, a known susceptibility gene of AA. This study provides further evidence for the association of previously reported genes with AA and novel findings such as *HLA-DRB5*, which might represent a hidden culprit gene for AU.

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Exomic Sequencing of Immune-Related Genes Reveals Novel Candidate Variants Associated with Alopecia Universalis

Seungbok Lee[1,2*], Seung Hwan Paik[3*], Hyun-Jin Kim[1,2], Hyeong Ho Ryu[3], Soeun Cha[1], Seong Jin Jo[3], Hee Chul Eun[3,4,5], Jeong-Sun Seo[1,2,6,7,8], Jong-Il Kim[1,2,6,7*], Oh Sang Kwon[3,4,5*]

Table 1. Demographic data of enrolled patients.

Age, years		3–43 (mean: 15)
Gender, n	Male	13 (65%)
	Female	7 (35%)
Onset, n[1]	Early onset	15 (75%)
	Late onset	5 (25%)
Disease duration, years		1–18 (mean: 5.5)
Nail dystrophy, n		6 (30%)
Family history, n		6 (30%)
Comorbid disorders, n	Atopy	2 (10%)
	Thyroid disease	2 (10%)
	Psoriasis	1 (5%)

6 samples of AU: Whole-exome seq

26 variants in immune-related genes as candidate

14 samples of AU: replication
155 Asian control

6 genes
HLA-DRB5
BTNL2
HLA-DMB
TLR1
PMS2
HLA-A

Study design

1. 100 case / 100 control exome sequencing
→ Validation, replication

2. 50 case / 50 control exome sequencing
→ Validation, replication

3. 50 case exome sequencing/ control (400명 질병관리본부: alopecia areata 유무는 모름)
→ Validation, replication

CNU 충남대학교병원

Enroll patients

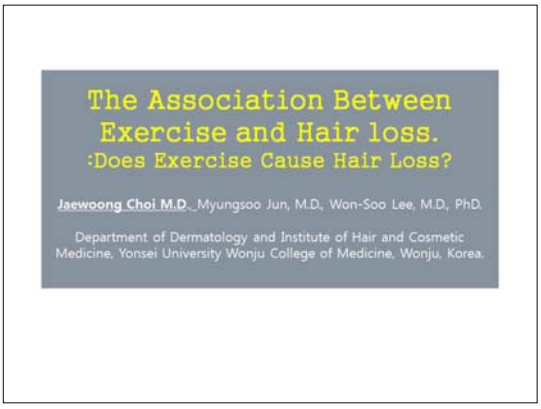
1. Alopecia totalis, alopecia universalis : 50 cases
2. With family history: yes or no
3. Early age of onset

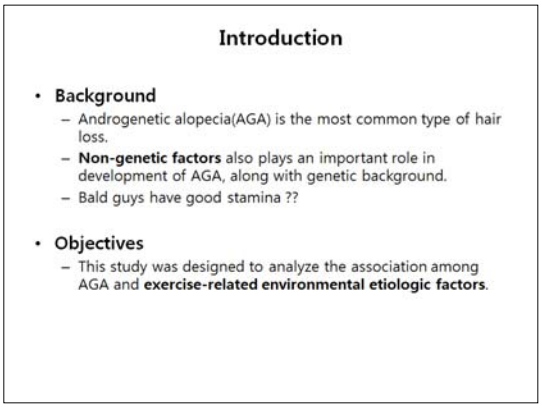
CNU 충남대학교병원

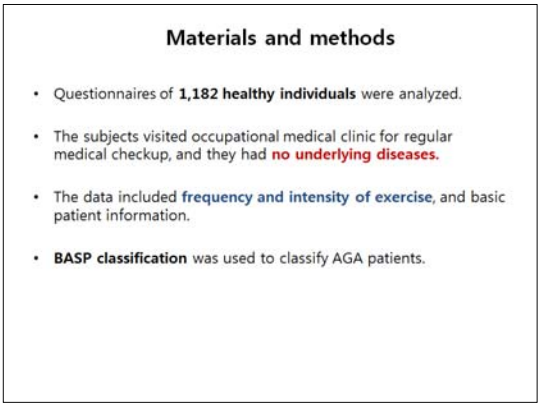
The association between exercise and hair loss: Does exercise cause hair loss?

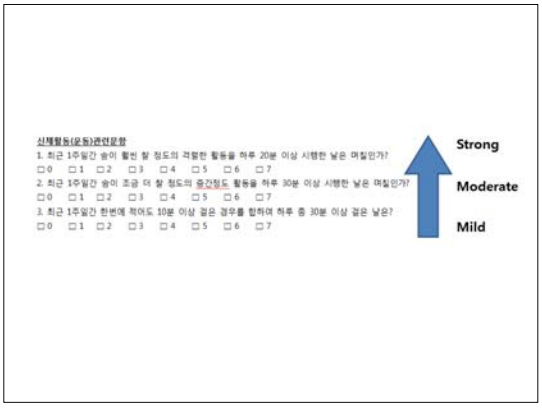
Jaewoong Choi, Myungsoo Jun, Won-Soo Lee

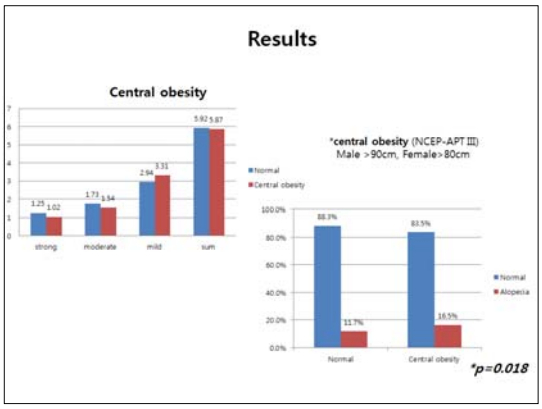
Department of Dermatology and Institute of Hair and Cosmetic Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea.

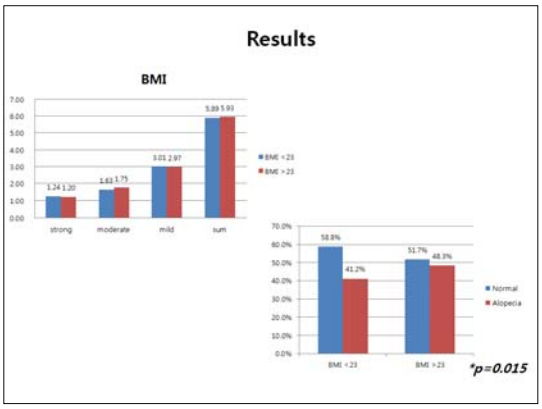


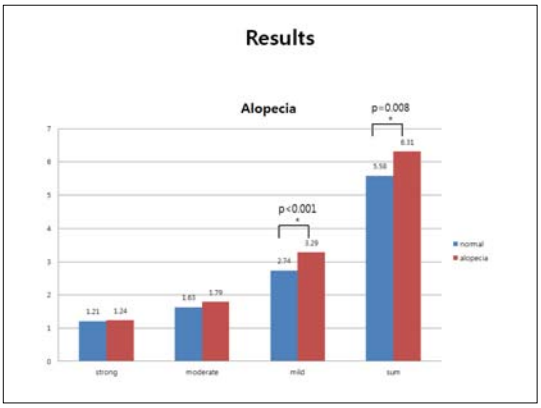


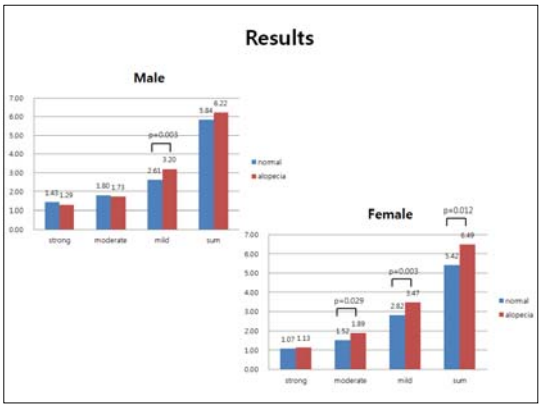


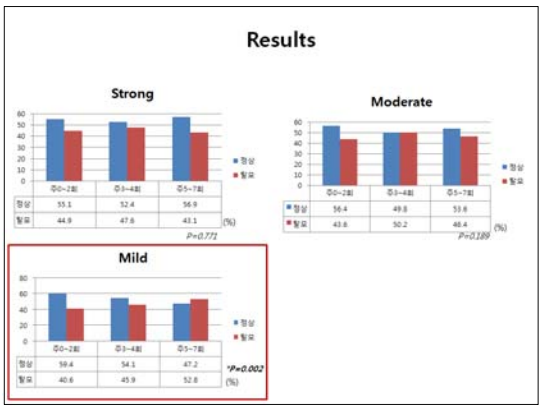


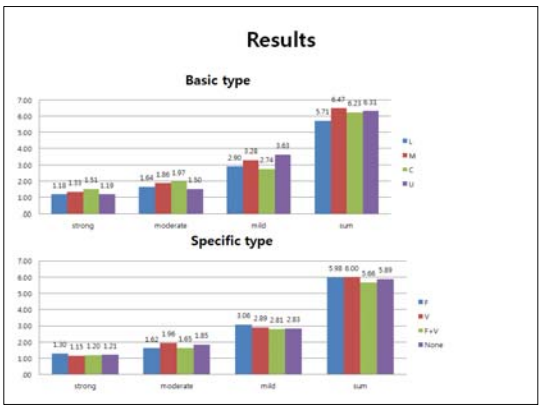

Results
Central obesity
*central obesity (NCEP-APT III)
Male >90cm, Female>80cm
Normal
Central obesity
strong
moderate
mild
sum
Normal
Alopecia
*p=0.018


Results
BMI
BMI <23
BMI >23
strong
moderate
mild
sum
Normal
Alopecia
*p=0.015

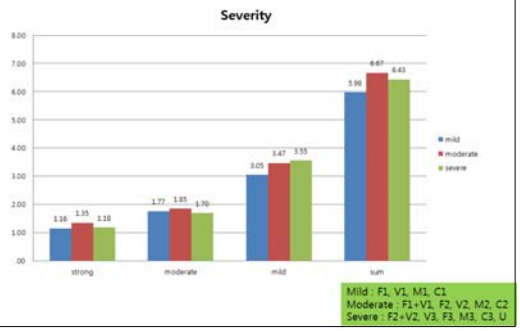

Results
Alopecia
p<0.001
p=0.008
normal
alopecia
strong
moderate
mild
sum


Results
Male
Female
p=0.005
p=0.012
p=0.029
p=0.003
normal
alopecia
strong
moderate
mild
sum


Results
Strong
Moderate
Mild
정상
탈모
P=0.771
P=0.189
*P=0.002


Results
Basic type
Specific type
L
M
C
U
F
V
F+V
None
strong
moderate
mild
sum

Results



Mild : F1, V1, M1, C1
Moderate : F1+V1, F2, V2, M2, C2
Severe : F2+V2, V3, F3, M3, C3, U

Discussion

- Alopecia patients **exercise more** than normal population(p=0.008).
- In male alopecia group, the frequency of **mild intensity of exercise** was significantly higher(p=0.03) than normal group.
- In female alopecia group, the frequency of **mild and moderate intensity of exercise** was significantly higher(p=0.029).
- According to the BASP classification, there was no difference among basic type groups.
- On the other hands, the frequency of exercise showed no statistically significant correlations, neither did the severity of AGA.

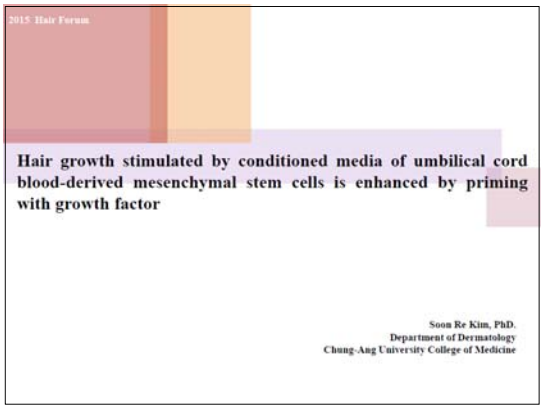
Conclusion

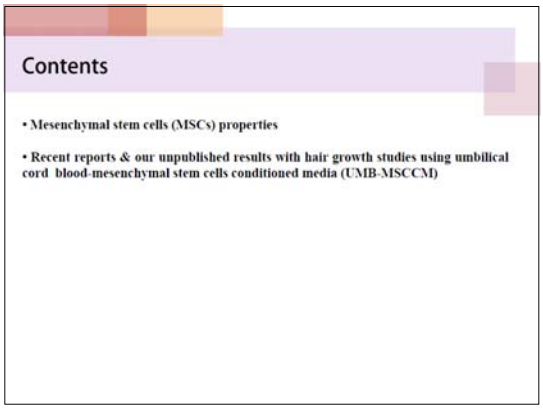
- This is the first large-scaled study designed to analyze the association between exercise and alopecia.
- According to the result, the **frequency of exercise was higher** in alopecia patients, especially when it comes to **mild exercise.**
- Limitaions
  - No hormonal study.
  - Further study designed for pathophysiology is necessary.

Hair growth stimulated by conditioned media of umbilical cord blood-derived mesenchymal stem cells is enhanced by priming with growth factor

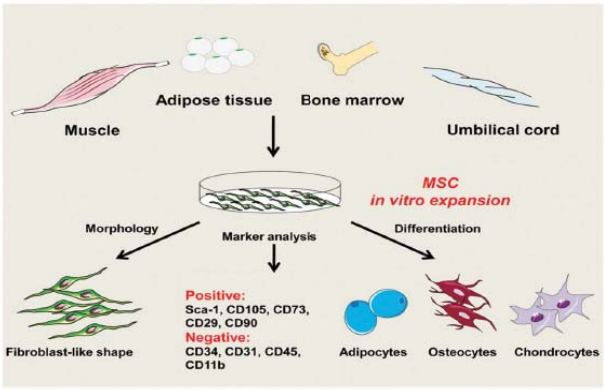
Soon Re Kim

Department of Dermatology Chung-Ang University College of Medicine





The properties of MSCs



• MSCs can isolated from various tissues including adipose, bone marrow, umbilical cord, muscle and tooth root.

Cell Death and Differentiation (2014) 21, 216–225

Tissue reparative properties of MSCs

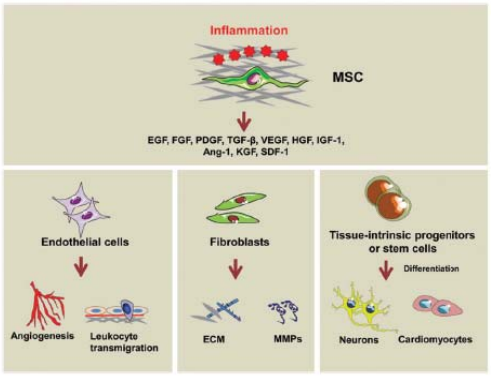
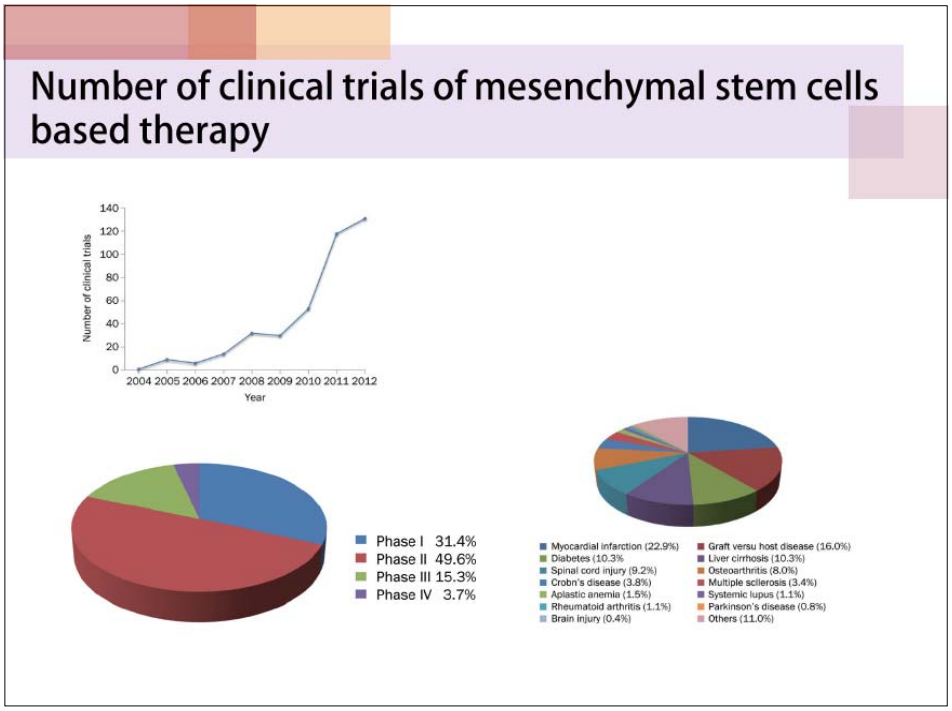


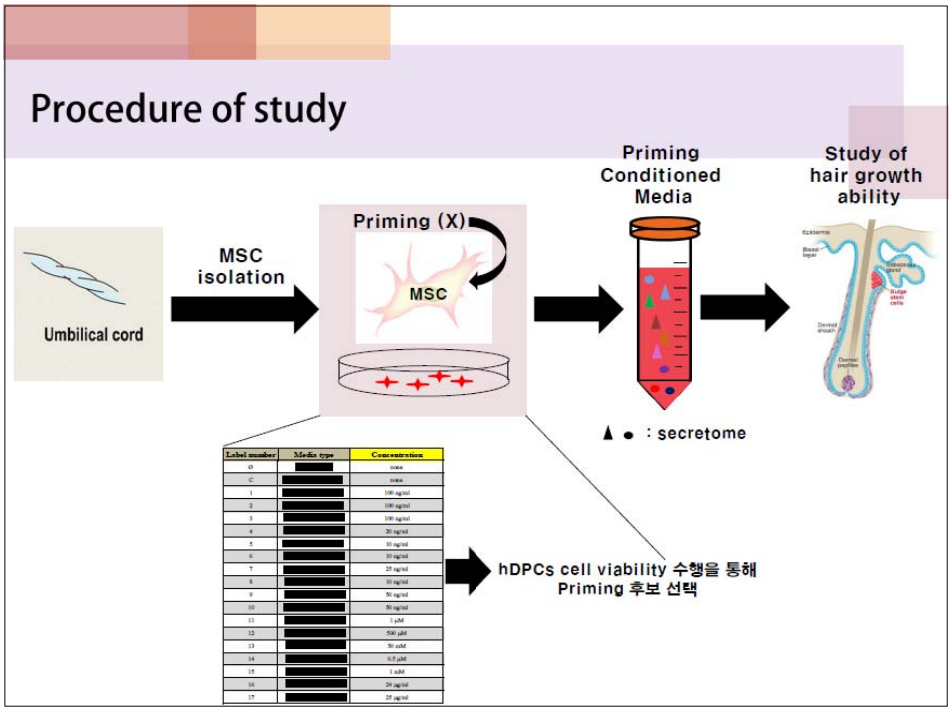
Table 1 Summary of growth factors critical for MSC-mediated tissue repair

Growth factors	Roles in MSC-mediated tissue repair
EGF	Wound healing,[114] tissue regeneration,[115,116] neurogenesis[117]
PDGF	Tissue repair[118]
FGF	Tissue repair,[114] intrinsic stem cell survival and regeneration[119]
TGF-β	Wound healing[120,121]
VEGF	Angiogenesis, wound healing[121–123]
HGF	Vasculogenesis,[124] intrinsic neural cell regeneration[34]
IGF-1	Wound healing,[114] neurogenesis[125]
KGF	Wound healing[126]
Ang-1	Angiogenesis, tissue repair[123]
EPO	Angiogenesis[127]
GDNF	Neuroprotective effect[128]
SDF-1	Neuroprotective effect,[129] wound healing[130,131]
IL-8	Wound healing[114]

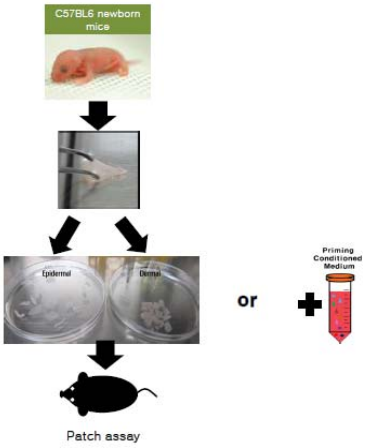
• The immunoregulatory properties and the tissue reparative functions of mesenchymal stem cells are induced by inflammatory cytokines.
• MSCs express immunosuppressive molecules and various growth factors that facilitate tissue repair and maintain immune homeostasis.

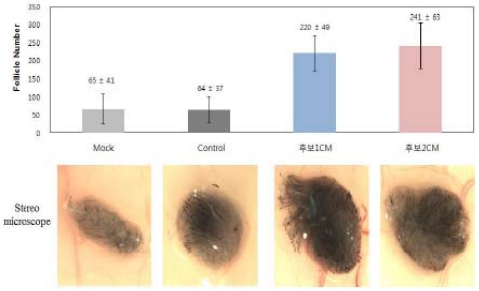
Cell Death and Differentiation (2014) 21, 216–225


Number of clinical trials of mesenchymal stem cells based therapy
Number of clinical trials
140
120
100
80
60
40
20
0
2004 2005 2006 2007 2008 2009 2010 2011 2012
Year
Phase I 31.4%
Phase II 49.6%
Phase III 15.3%
Phase IV 3.7%
Myocardial infarction (22.9%)
Diabetes (10.3%
Spinal cord injury (9.2%)
Crobn's disease (3.8%)
Aplastic anemia (1.5%)
Rheumatoid arthritis (1.1%)
Brain injury (0.4%)
Graft versu host disease (16.0%)
Liver cirrhosis (10.3%)
Osteoarthritis (8.0%)
Multiple sclerosis (3.4%)
Systemic lupus (1.1%)
Parkinson's disease (0.8%)
Others (11.0%)

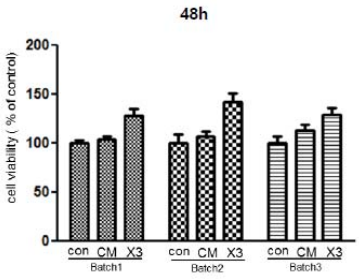

Procedure of study
Umbilical cord
MSC isolation
Priming (X)
MSC
Priming Conditioned Media
Study of hair growth ability
▲ ● : secretome
hDPCs cell viability 수행을 통해
Priming 후보 선택

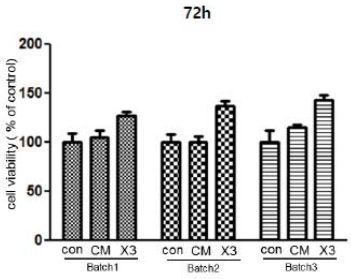
Patch assay



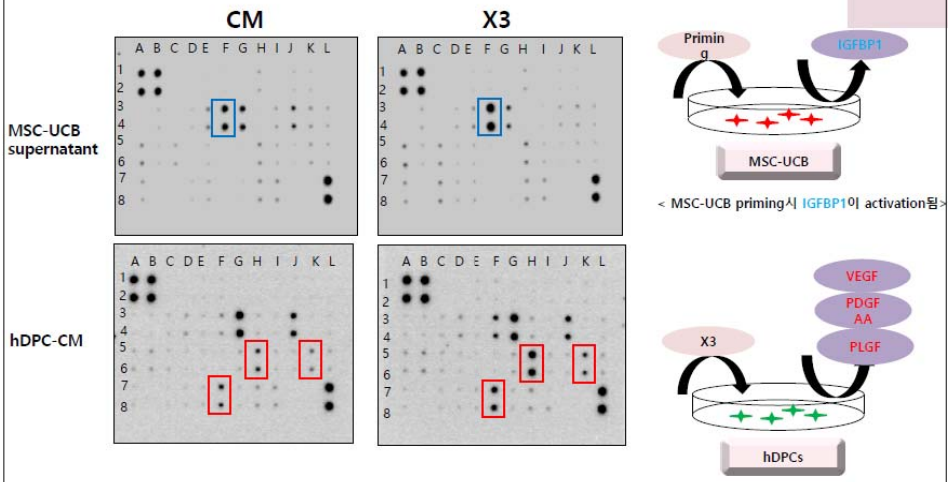


Cell viability assay





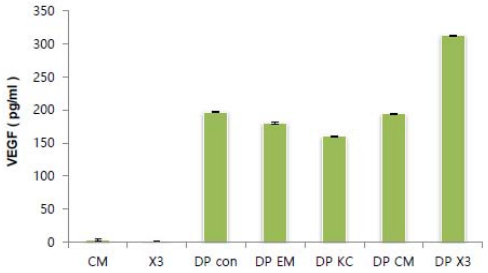
Growth factor array



VEGF ELSIA assay

◈ Condition

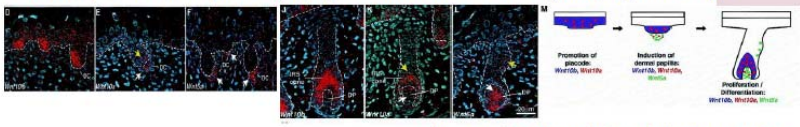
CM: CM only
X3: X3 CM only
DP con: hDPCs + DMEM supernatanat
DP EM: hDPCs + control media (Empty Media)
DP KC: hDPCs+ keratinocyte priming media
DP CM: hDPCs + conditioned media
DP X3: hDPCs + MSC priming media



Hair follicle regeneration과 Wnt5A, Versican, VEGF 연관성

Expression of *Wnts10b, 10a* and *5a* is specifically upregulated in hair follicles at early morphogenetic stages

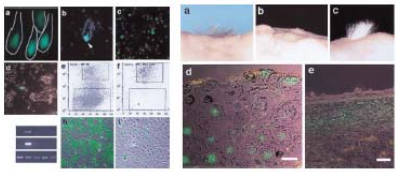
Wnt5A



Seshamma Reddy et.al, Mechanisms of development, 2001

Versican Expression Coincided with in Vivo Dermal Condensation and Hair-Inductive Ability.

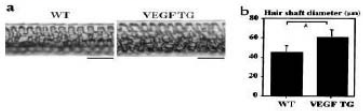
Versican



JIRO KISHIMOTO, Proc. Natl. Acad. Sci. USA 96 (1999)

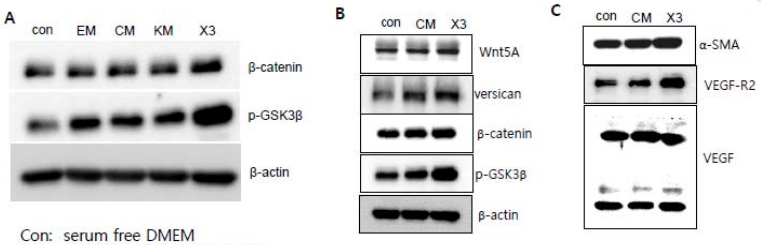
Accelerated hair regrowth and increased follicle size in VEGF transgenic mice.

VEGF



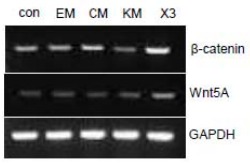
J Clin Invest. 2001 Feb 15; 107(4): 409–417.

Protein 발현 조절



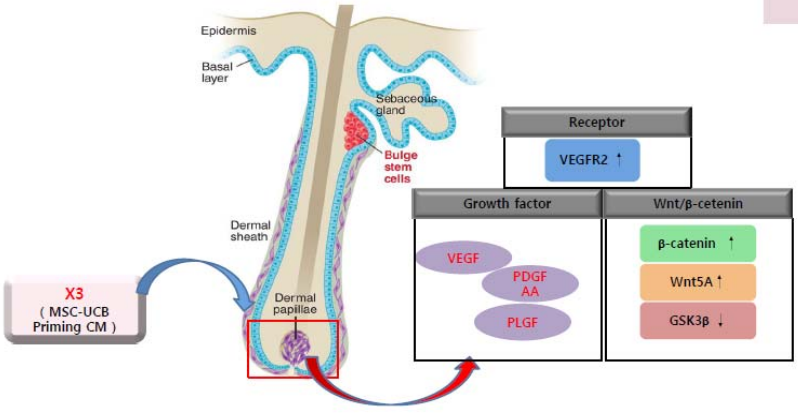
Con: serum free DMEM
EM: control media (Empty Media)
CM: conditioned media
KC: keratinocyte priming media
X3: MSC Priming media

β-catenin, Wnt5A mRNA expression



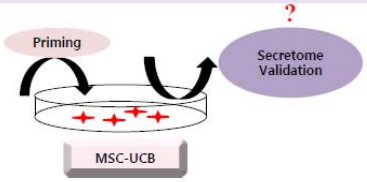
Con: serum free DMEM
EM: control media (Empty Media)
CM: conditioned media
KC: keratinocyte priming media
X3: MSC Priming media

Priming CM에 의한 dermal papilla regulation factor



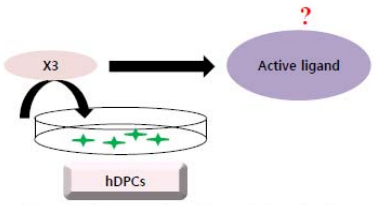
Further study

1.



▶ Secretome validation for MSC-UCB standardization

2.



▶ What is the active ligand for hair growth regulation?

3. Cultured human dermal papilla cell을 이용한 모낭 성장 ability 확인

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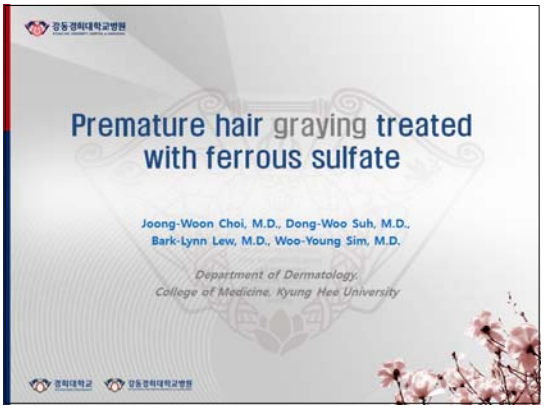
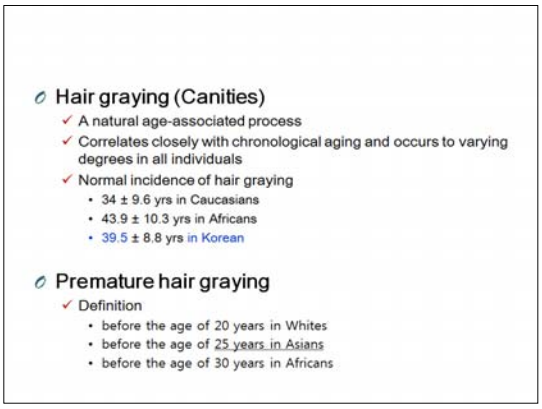
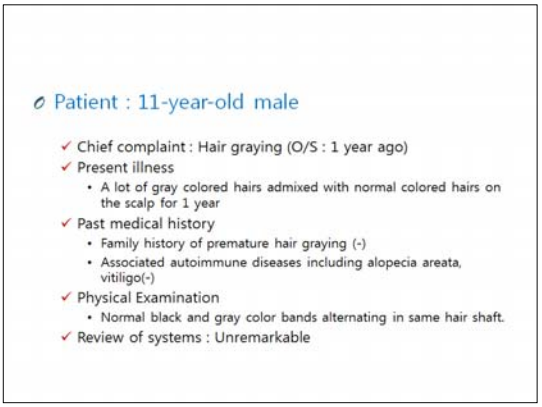
Premature hair graying treated with ferrous sulfate

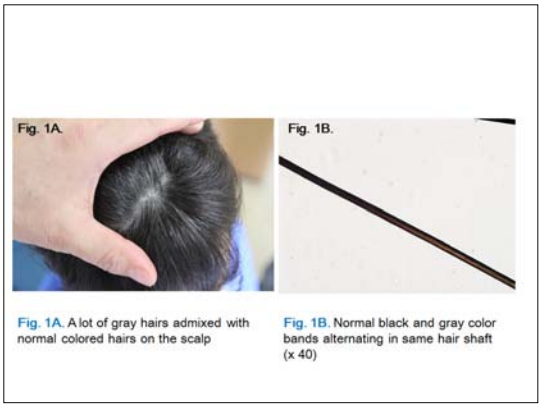
Joong-Woon Choi, Dong-Woo Suh, Bark-Lynn Lew, Woo-Young Sim

Department of Dermatology, College of Medicine, Kyung Hee University









Initial lab.

- ✓ Hb 8.4 g/dL ↓ Hct 27.9 % ↓
- ✓ MCV 56.1 fL ↓ MCH 17.0 pg ↓ MCHC 30.3 g/dL ↓
- ✓ Ferritin 2.6 ng/mL ↓

→ **Iron deficiency anemia, suspected**

Treatment & Course

- ✓ Iron supplements for 5 months
  - Ferrous sulfate (40mg/day)
- ✓ After 5 months of treatment, his hair color recovers nearly normal black color
- ✓ No recurrence or aggravation until now

Fig. 1A. Before treatment, a lots of gray hairs were observed within normal hairs on the scalp.

Fig. 2. After 5 months of iron supplement treatment, his hair color recovered nearly normal black color.

Causes of premature hair graying

- ✓ Autoimmune disorders
  - pernicious anemia, hyper- or hypothyroidism, atopic diathesis, vitiligo, progeroid syndromes
- ✓ Nutritional deficiencies
  - chronic protein loss (kwashiorkor, nephrosis,celiac disease), severe iron deficiency and copper deficiency
- ✓ Stress
- ✓ Certain drugs
  - chloroquine, mephenesin, phenylthiourea, triparanol, fluorobutyrophenone, dixyrazine, the epidermal growth factor receptor inhibitor imatinib and interferon-alpha etc.
- ✓ HIV infection, cystic fibrosis, and Hodgkin's lymphoma

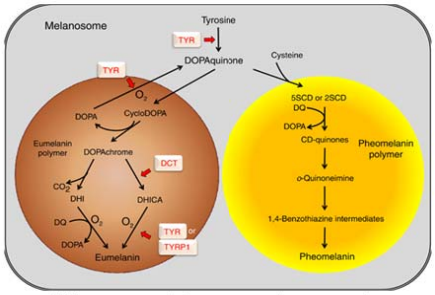
Table 1: Syndromes manifesting with premature graying of hair[14,18,22-24]

Name	Inheritance	Pattern/associated complaints/presentation
Book's syndrome	AD	Premolar hypodontia/bicuspid hypoplasia, palmoplantar hyperhidrosis
Progeria	AD	By 2 years of age, only sparse gray or white hair seen with plucked bird facies, joint stiffness, abnormal dentition, loss of subcutaneous fat
Pangeria (Werner's syndrome)	AR	Temporal graying starts in adolescence or as early as 8 years of age, further spreads across the entire scalp accompanied by progressive baldness by 25 years of age with sclerodermoid skin changes, beak-shaped nose, short stature
Dystrophia myotonica	AD	Graying of hair followed by myotonia and muscle wasting, cataracts
Rothmund–Thompson syndrome	AR	Rapidly progressive premature canities in adolescence with poikiloderma, photosensitivity, alopecia, cataract, short stature
Cri-du-chat syndrome	Most cases due to sporadic de novo deletion of 5p arm	Premature canities seen in one-third of patients with microcephaly, hypotonia, and characteristic facies
Ataxia telangiectasia	AR	Cerebellar ataxia, immunodeficiency, ocular telangiectasia
Fisch's syndrome	NK	Early extensive premature canities with impaired hearing and partial heterochromia iridis
Seckle syndrome (bird-headed dwarfism	AR	Bird-headed profile, trident hands, skeletal defects, hypodontia, pancytopenia
Down's syndrome	Sporadic	Premature canities seen in 14% patients

AD: Autosomal dominant, AR: Autosomal recessive, NK: Not known

Pathogenesis of gray hairs

- ✓ Graying is understood as a loss of pigment in the shaft (Tobin and Paus 2001)
- ✓ Gray hair has undergone a marked reduction in melanogenically-active melanocytes in the hair follicle (Commo et al 2004).
  - The net effect of this reduction is that fewer melanosomes are incorporated into cortical keratinocytes of the hair shaft.
- ✓ There appears also to be a defect of melanosome transfer.
  - Due to either defective melanosomal transfer to the cortical keratinocytes or melanin incontinence due to melanocyte degeneration.



Premature canities and trace elements

- ✓ Trace elements needs in the pathway of melanogenesis
  - Copper : required for tyrosinase activity
  - Zinc : TRP-2 (tyrosinase related protein-2) enzyme activity
- ✓ **Iron**
  - Dopachrome tautomerase
  - Rearrangement of dopachrome to 5,6-dihydroxyindoles
  - Oxidative polymerization of the 5,6-dihydroxyindoles

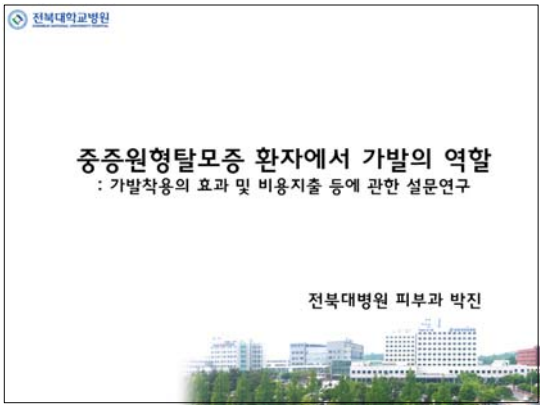
- We report a patient who had premature hair graying probably due to iron deficiency anemia treated successfully with iron supplements(ferrous sulfate).

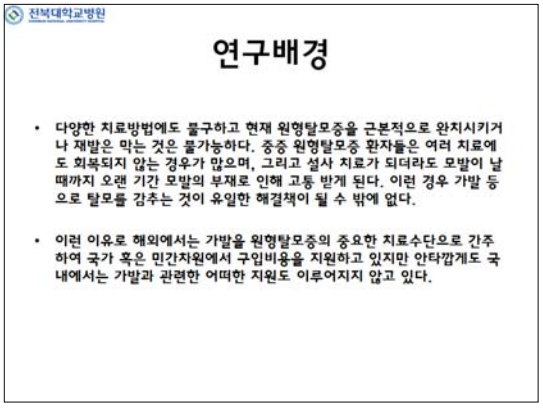
1. Tobin DJ, Paus R. Graying: Gerontobiology of the hair follicle pigmentary unit. Exp Gerontol 2001;36:29-54.
2. Patrick Henry McDonough, Robert A, Schwartz. Premature hair graying. Cutis 2012;89;161-165
3. Fatemi Naieni F, Ebrahimi B, Vakilian HR, Shahmoradi Z. Serum iron, zinc, and copper concentration in premature graying of hair. Biol Trace Elem Res 2012;146:30-4.
4. Bhat RM, Sharma R, Pinto AC, Dandekeri P, Martis J. Epidemiological and investigative study of premature graying of hair in higher secondary and pre-university school children. Int J Trichol 2013;5:17-21.
5. Chakraborty AK, Orlow SJ, Pawelek JM (1992) Evidence that dopachrome tautomerase is a ferrous iron-binding glycoprotein. FEBS Lett 302(2):126–128

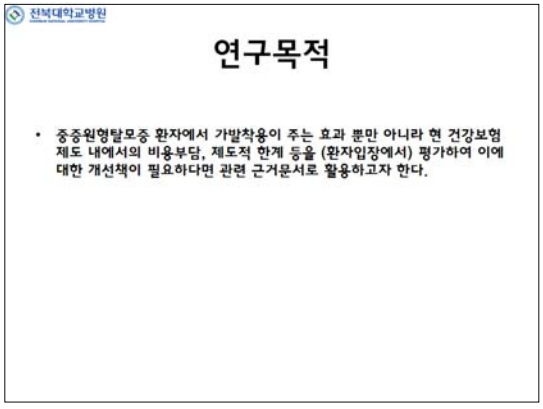
중증원형탈모증 환자에서 가발의 역할: 가발착용의 효과 및 비용지출 등에 관한 설문연구

전북대학교 의과대학 피부과학교실

박 진







전북대학교병원

연구대상

- 치료목적의 가발을 착용한 경험이 있는 중증원형탈모증 환자
  - 1) 만 5세~70세
  - 2) SALT 〉 50%
  - 3) 가발착용 기간이 최소 2주 이상
- 연구대상자 수: 50명 ± 10명 (현재 30명 모집)

**본 연구는 전북대병원 연구윤리심의위원회의 승인을 받았음.

전북대학교병원

연구방법 (설문연구)

- 1) 인구학적 정보
  - 성별, 연령, 학력, 직업, 결혼여부, 소득수준, 야외활동성향 등
- 2) 가발 구매, 착용 및 관리행태
  - 가발착용동기, 구입처, 가발정보 습득경로, 가발가격, 착용기간, 가발소유 개수, 교체주기, 관리빈도, 개선점
- 3) 가발 관련 현 의료제도 및 정책에 대한 인식
  - 치료목적의 가발착용, 가발교육, 정부지원의 필요성, 구체적 지원 방법 등
- 4) 가발착용의 생물학적 효과 (BIQ) (가발착용 전후)
- 5) 가발착용의 삶의 질에 대한 영향 (Skindex-29) (가발착용 전후)
- 6) 가발착용(보조기기)의 정신사회적 영향 (PIADS)

전북대학교병원

연구방법

- *PIADS (Psychosocial impact of assistive device scale)*
  - *26개 항목으로 구성된 보조공학기기의 심리사회적 영향 척도*
  - *기능적 독립성, 안녕 및 삶의 질에 대한 보조기기의 효과를 평가*
  - *1) 자기욱구실현능력 (competence, 12항목): 자기욱구실현, 생산성, 등*
  - *2) 적응성 (adaptability, 6항목): 공동체 참여능력, 진취적 태도 등*
  - *3) 자존감 (self-esteem, 8항목) : 자존감, 안전감, 자신감 등*
  - *점수체계: -3(가장 부정적) ~ +3(가장 긍정적)*

제오영 등. Psychosocial Impact of Assistive Devices Scale (PIADS)의 국내 적용을 위한 탄탄연구. 대한임상피부학회지 2008;16(3):71-89.
Inui et al, Psychosocial impact of wigs or hairpieces on perceived quality of life level in female patients with alopecia areata., J Dermatol 2013; 40(3):229-4.

전북대학교병원

연구결과 (1): 인구학적 정보

- 성별: 여자
- 연령: 10-19세
- 직업: 학생

특성	구분	N	%
성별	남자	7	23.3
	여자	23	76.7
연령	10-19세	9	30.0
	20-29세	5	16.7
	30-39세	5	16.7
	40-49세	6	20.0
	50세 이상	5	16.7
학력	의무교육 재학	3	10.0
	중학교 졸업 이하	3	10.0
	고등학교 재학	6	20.0
	고등학교 졸업	5	16.7
	대학교 재학-중업	9	30.0
	대학원 재학-중업	4	13.3
직업	사무직	2	6.7
	전문직	5	16.7
	판매서비스직	6	20.0
	학생	10	33.3
	주부 및 기타	7	23.3

특성	구분	N	%
결혼여부	미혼	15	50.0
	기혼	15	50.0
종교	개신교	10	33.3
	천주교	6	20.0
	불교	2	6.7
	기타 및 무교	12	40.0
가구 월소득	100만원 미만	2	6.7
	101-300만원	13	43.3
	301-500만원	6	20.0
	501만원 이상	4	13.3
	무응답	5	16.7
신체활동	전혀 하지 않는다	2	6.7
	주 1-2회	17	56.7
	주 3-4회	6	20.0
	주 5회 이상	5	16.7
성격유형	내성적	6	20.0
	보통	18	60.0
	외향적	6	20.0
전체		30	100.0

전북대학교병원

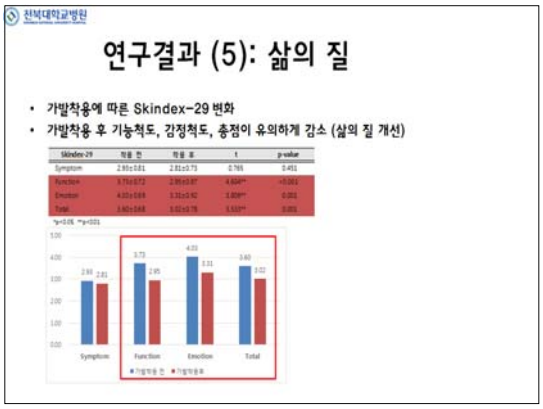
연구결과 (2): 가발구입, 착용 및 관리

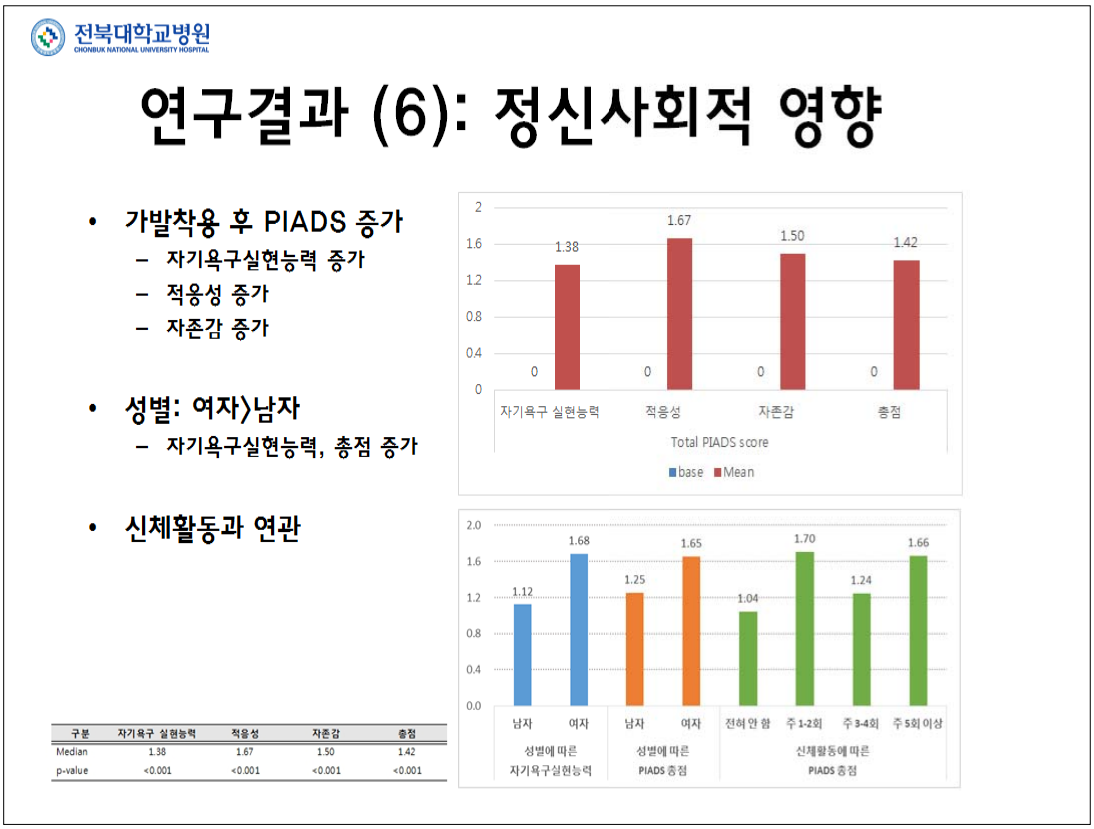
- 종류: 인모(맞춤)〉인조모〉인모(기성)
- 착용이유: 본인의사〉〉〉의료진
- 구입처: 가발전문점
- 가발정보습득: 인터넷〉〉〉의료진
- 가격: 101-150만원, 10만원 이하
- 착용기간: 2년 이상
- 교체주기: 6개월 미만

전북대학교병원

연구결과 (3): 가발 제도 및 정책

- 가발은 의학적으로 반드시 필요하다.
- 가발구입 시 정부지원이 필요하다
  - 두피모발 50%이상 빠진 환자, 가발구입 전액 현금지급, 10-30만원, 6개월마다
- 가발에 대한 정보를 의료진이 제공해야 한다.





구분	자기욕구 실현능력	적응성	자존감	총점
Median	1.38	1.67	1.50	1.42
p-value	<0.001	<0.001	<0.001	<0.001

전북대학교병원 CHONBUK NATIONAL UNIVERSITY HOSPITAL

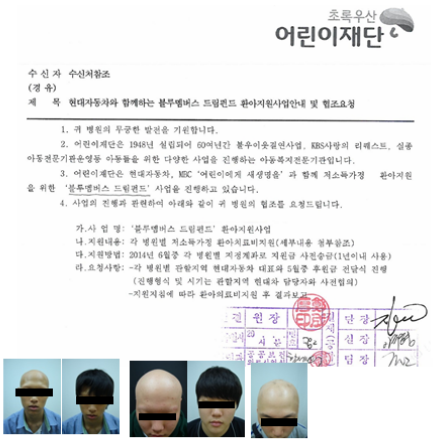
원형탈모환자의 가발지원 현황

국가	주도	대상	지원내용
미국	일부 주정부 (미네소타, 뉴햄프셔주 등)		최대 $350/yr 현금지급
	NAAF (Ascot fund)		최대 500$/회 지원
	가발회사(DU-USA, Godiva's Secret Wig, Lori's Wig, etc)		5~25% 할인
호주	연방정부		의료보장구에 대한 세금면제 ($1000이상 소요비용 실비로 환불)
	일부 주정부 (South Wales, South Austrailia, Vicotoria 등)		보조금 지급 (예, 인조모: $240/2yrs, 인모: $600/2yrs)
	보험회사		회사 기준에 따라 가발구입비용 환급
뉴질랜드	정부		보조금 지급 (성인: 알과성 $408.88/.yr, 영구: $2330.66/9yrs, 소아(18세이하): $1226.66/3yrs)
영국	정부(NHS)	소아 및 청소년 (16세 이하), 입원환자, 국가유공자 등	가발종류에 따라 차등하여 가발구입비 지원 (인조모:£27.05 27.05~ 인모(맞춤): £258.35)
	영국피부과의사회	60세 미만	가발구입비 혹은 부가세 감면혜택(?)
한국	정부		-
	전북대병원 피부과 & 전북사회복지공공모금회	전북지역 거주 저소득층 중증원형탈모증환자	맞춤가발(인모) 무상지급

전북대학교병원 CHONBUK NATIONAL UNIVERSITY HOSPITAL

중증원형탈모환자를 위한 가발지원사업 (전북대병원 피부과)

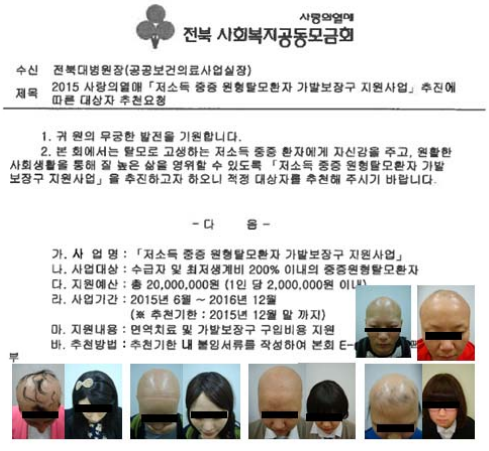
- 2014년: 초록우산 어린이재단 연계 (소아 3명)
- 2015년: 사랑의 열매 전북 사회복지공공모금회 (저소득층 10명)


초록우산 어린이재단

수 신 자 수신처참조
(경 유)
제 목 현대자동차와 함께하는 붉루벨버스 드림랜드 환아지원사업안내 및 협조요청

1. 귀 병원의 무궁한 발전을 기원합니다.
2. 어린이재단은 1948년 설립되어 60여년간 불우이웃결연사업, KBS사랑의 리퀘스트, 실종아동전문기관운영등 아동들을 위한 다양한 사업을 진행하는 아동복지전문기관입니다.
3. 어린이재단은 현대자동차, MBC '어린이에게 새생명을' 과 함께 저소득가정 환아지원을 위한 '붉루벨버스 드림랜드' 사업을 진행하고 있습니다.
4. 사업의 진행과 원활하여 아래와 같이 귀 병원의 협조를 요청드립니다.

가.사 업 명: '붉루벨버스 드림랜드' 환아지원사업
나.지원내용: 각 병원별 저소득가정 환아치료비지원(세부내용 첨부참조)
다.지원방법: 2014년 6월중 각 병원별 지정계좌로 지원금 사전송금(1년이내 사용)
라.요청사항: -각 병원별 관할지역 현대자동차 대표와 5월중 후원금 전달식 진행
(진행형식 및 시기는 관할지역 현대자동차 담당자와 사전협의)
-지원자심에 따라 환아의료비지원 후 결과보고

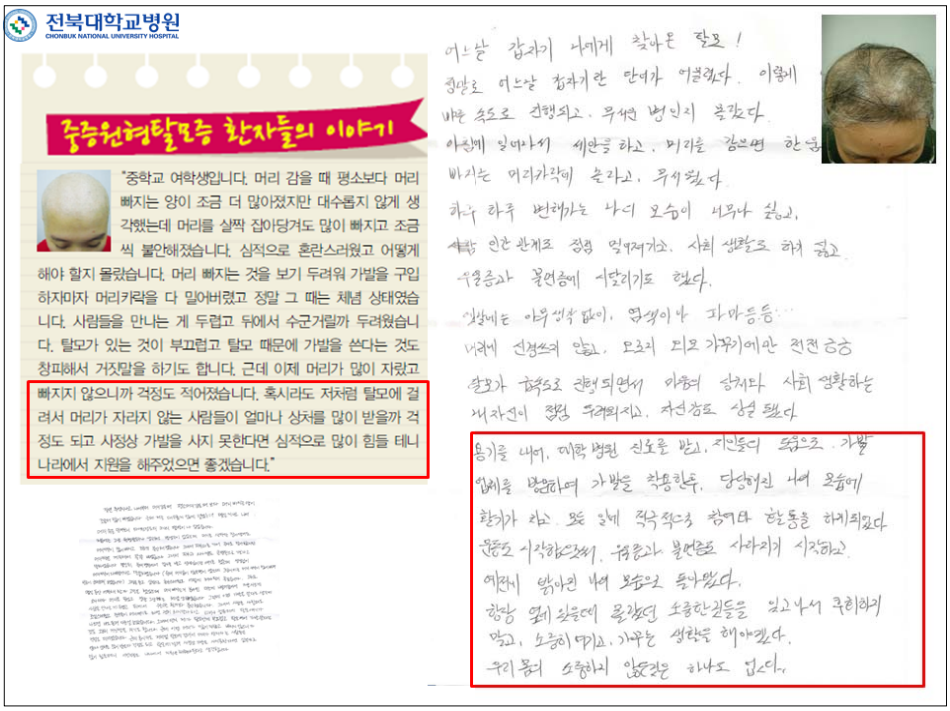

사랑의열매 전북 사회복지공동모금회

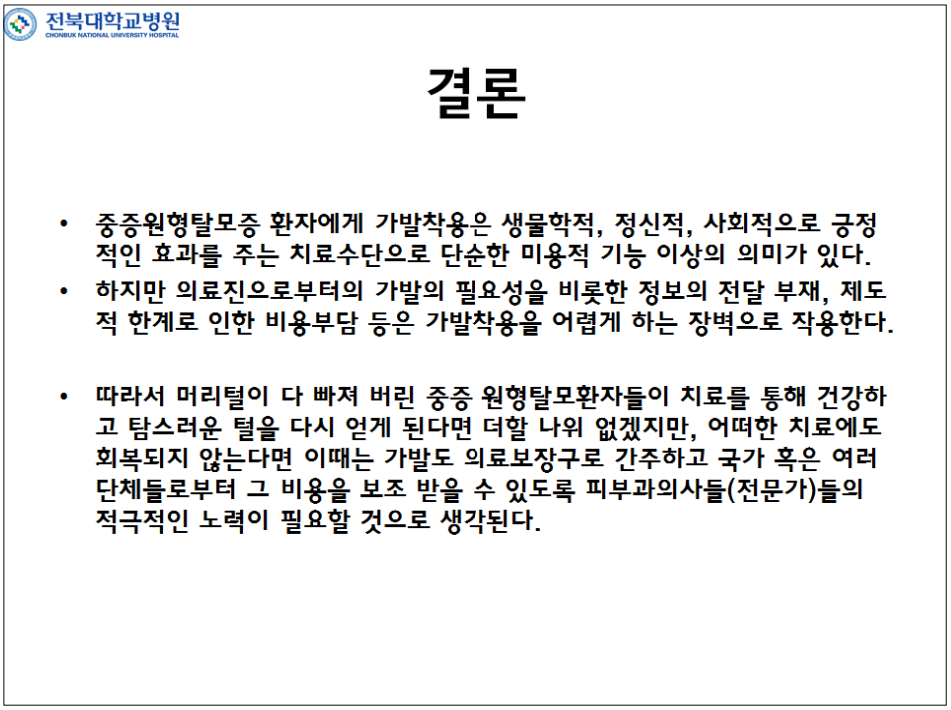
수신 전북대병원장(공공보건의료사업실장)
제목 2015 사랑의열매「저소득 중증 원형탈모환자 가발보장구 지원사업」추진에 따른 대상자 추천요청

1. 귀 원의 무궁한 발전을 기원합니다.
2. 본 회에서는 탈모로 고생하는 저소득 중증 환자에게 자신감을 주고, 원활한 사회생활을 통해 질 높은 삶을 영위할 수 있도록 「저소득 중증 원형탈모환자 가발보장구 지원사업」을 추진하고자 하오니 적정 대상자를 추천해 주시기 바랍니다.

- 다 음 -

가. 사 업 명 : 「저소득 중증 원형탈모환자 가발보장구 지원사업」
나. 사업대상 : 수급자 및 최저생계비 200% 이내의 중증원형탈모환자
다. 지원예산 : 총 20,000,000원 (1인 당 2,000,000원 이내)
라. 사업기간 : 2015년 6월 ~ 2016년 12월
(※ 추천기한 : 2015년 12월 말 까지)
마. 지원내용 : 면역치료 및 가발보장구 구입비용 지원
바. 추천방법 : 추천기한 내 붙임서류를 작성하여 본회 E-


전북대학교병원
CHONBUK NATIONAL UNIVERSITY HOSPITAL
중증원형탈모증 환자들의 이야기
"중학교 여학생입니다. 머리 감을 때 평소보다 머리 빠지는 양이 조금 더 많이졌지만 대수롭지 않게 생각했는데 머리를 살짝 잡아당겨도 많이 빠지고 조금씩 불안해졌습니다. 심적으로 혼란스러웠고 어떻게 해야 할지 몰랐습니다. 머리 빠지는 것을 보기 두려워 가발을 구입하지마자 머리카락을 다 밀어버렸고 정말 그 때는 체념 상태였습니다. 사람들을 만나는 게 두렵고 뒤에서 수군거릴까 두려웠습니다. 탈모가 있는 것이 부끄럽고 탈모 때문에 가발을 쓴다는 것도 창피해서 거짓말을 하기도 합니다. 근데 이제 머리가 많이 자랐고 빠지지 않으니까 걱정도 적어졌습니다. 혹시라도 저처럼 탈모에 걸려서 머리가 자라지 않는 사람들이 얼마나 상처를 많이 받을까 걱정도 되고 사정상 가발을 사지 못한다면 심적으로 많이 힘들 테니 나라에서 지원을 해주었으면 좋겠습니다."


전북대학교병원
CHONBUK NATIONAL UNIVERSITY HOSPITAL
결론
• 중증원형탈모증 환자에게 가발착용은 생물학적, 정신적, 사회적으로 긍정적인 효과를 주는 치료수단으로 단순한 미용적 기능 이상의 의미가 있다.
• 하지만 의료진으로부터의 가발의 필요성을 비롯한 정보의 전달 부재, 제도적 한계로 인한 비용부담 등은 가발착용을 어렵게 하는 장벽으로 작용한다.
• 따라서 머리털이 다 빠져 버린 중증 원형탈모환자들이 치료를 통해 건강하고 탐스러운 털을 다시 얻게 된다면 더할 나위 없겠지만, 어떠한 치료에도 회복되지 않는다면 이때는 가발도 의료보장구로 간주하고 국가 혹은 여러 단체들로부터 그 비용을 보조 받을 수 있도록 피부과의사들(전문가)들의 적극적인 노력이 필요할 것으로 생각된다.

Pros and cons of the scalp medical tattoo

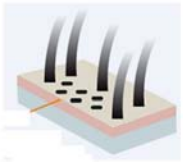
Jin Mo Park

Yonsei Mobelle Dermatologic and Hair transplantation Clinic

Pros and cons of the Scalp medical Tattoo

2015. 14th Hair forum
Yonsei Mobelle Dermatologic and Hair transplantation Clinic
Jin Mo Park, M.D., Ph.D.

Concept of SMT



2-Dimensional dot between 3-Dimensional hair
Semi-permanent

Semi vs Permanent

Duration
Component
Color
Allergy
Depth
Re-touch

Steps of SMT

1. Consult
2. Design & Photo
3. Anesthesia & Dressing
4. Tattooing
5. Post tattooing Tx
6. Re-touch

Side Effect

- Unnaturalness
- Discoloration
- Short lasting Duration
- Shock Hair loss
- Color spreading
- Dot coalescence

Factors influencing the result

- Dr's factor
  - High expectation
  - Insufficient explanation
  - Learning curve & Technique
- Patient's factor
  - High expectation
  - Scalp conditions
  - Others

Etc

2015

대한모발학회

제14차 Hair Forum

제 2 부 : 주제 발표 [백모]

The Korean Hair Research Society

■ **CURRICULUM VITAE** ■

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건선, 피부암, 피부종양, 피부외과, 항암제특이 피부반응, 모발생리

Hair graying: Clinical features and significance

서울대학교 의과대학 피부과학교실

조 성 진

HAIR GRAYING:
CLINICAL FEATURES AND SIGNIFICANCE

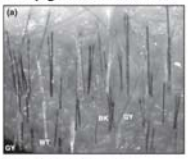
서울대학교병원 피부과
조성진

Ageing appearance of hair graying

- Hair-graying is one of the conspicuous signs of aging.
- Gray hair leads to cosmetic problem as it is more noticeable against dark hair.

Hair Graying

- Natural age-associated feature
- Loss of pigment in the shaft



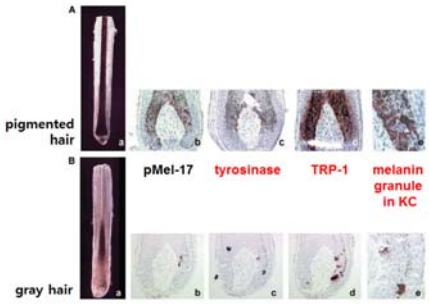
- Onset of hair graying
  - 34 ± 9.6 years of age in Caucasians
  - 4.9 ± 10.3 years in African Americans
  - 50% of people have 50% gray hair by 50 years of age

Graying
= white + gray hairs

Melanocytes in gray hair

Commo et al, 2004

Melanin synthesis and transfer in gray hair



Commo et al, 2004

Physical and chemical properties of gray hair

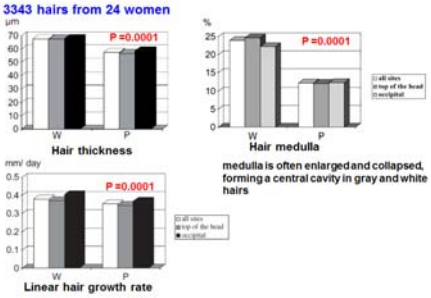
- **increased sensitivity to weathering**
- **increased cysteic acid residues and decreased cystine**
- **increased fiber reactivity to reducing and oxidizing agents**

Hollfelder et al. 1995

- **Reflection of a change in the chemical and physical properties of the post-pigmented hair fiber.**
  - Melanosome as 'regulatory packages'
    - Unpigmented hair exhibit a higher rate of hair fiber elongation
    - Pigmented hair shows early differentiation
    - Melanin granules: a buffer of calcium?
  - Various cytokines from MCs

White hair vs. Pigmented hair

3343 hairs from 24 women



medulla is often enlarged and collapsed, forming a central cavity in gray and white hairs

Van Neste. 2004

PROGRESSION OF HAIR GRAYING

Hair Graying Pattern Depends on Gender, Onset Age and Smoking Habits

Seong Jin Jo[1,2], Seung Hwan Paik[1], Jae Woo Choi[1], Jong Hee Lee[1,2], Soyun Cho[1,2], Kyu Han Kim[1,2], Hee Chul Eun[1,2] and Ok Sang Kwon[1,2]*

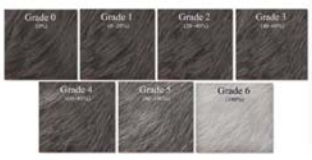
[1]Department of Dermatology, [2]Institute of Dermatological Science, Medical Research Center, Seoul National University College of Medicine, 101 Daehangno, Jongno-gu, Seoul 110-744, and [3]Department of Dermatology, SMG-SNU Boramae Medical Center, Seoul, Korea. *E-mail: okhwan@snu.ac.kr

Accepted April 28, 2011.

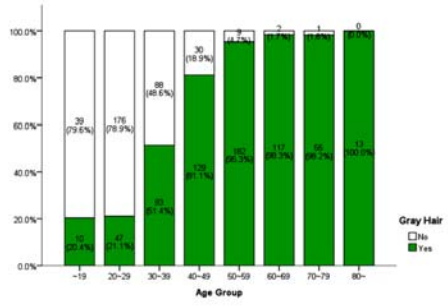
Acta Derm Venereol, 2012

Survey for gray hair

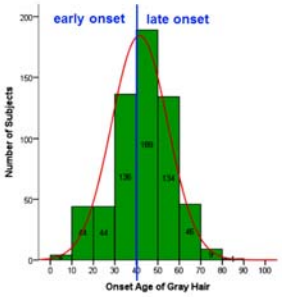
- **Subjects**
  - **Patients visiting out-patient clinic**
  - without pigment disorder
  - **1002 subjects**
- **Questionnaires**
- **Investigator's assessment**



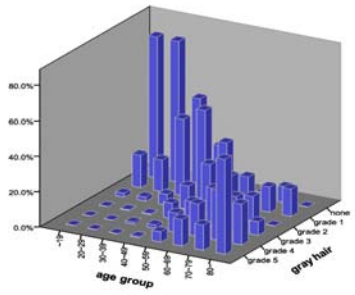
Prevalence of gray hair by age-group



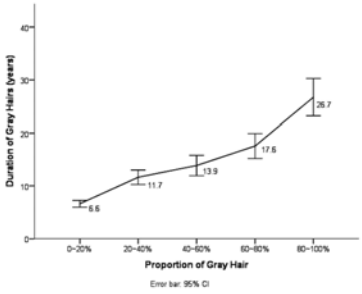
Onset of hair-graying



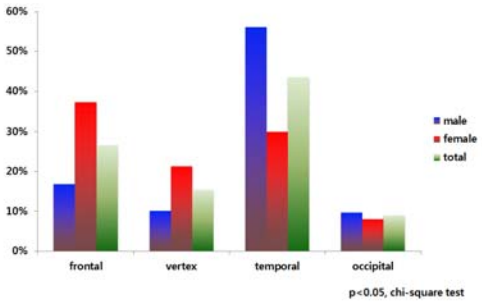
The extent of Grayness by age-group



Progression of gray hair

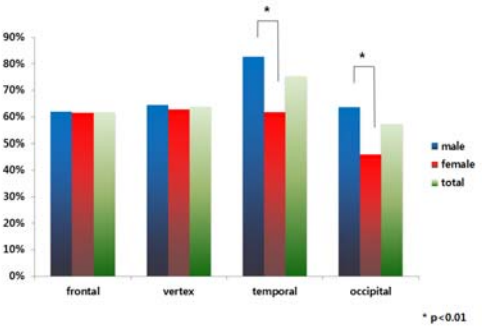


Initial involvement of gray hair



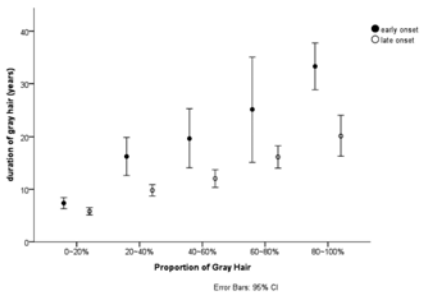
p<0.05, chi-square test

Involved area of gray hair

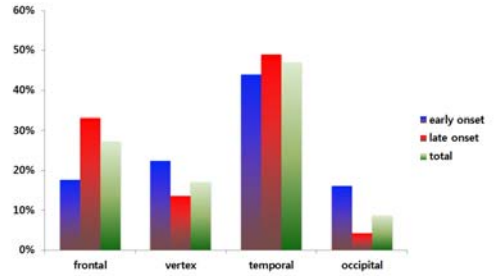


* p<0.01

Early-onset hair graying



Initially involved area : Early onset vs. late onset



p<0.05, chi-square test

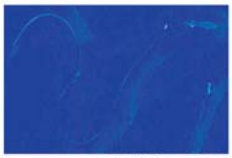
Risk factors of gray hair

	OR	p-value	95% CI of OR Lower	Upper
For hair graying				
Age	1.149	< 0.001	1.126	1.172
Smoking behavior (smoker)	1.993	0.008	1.201	3.307
For early-onset hair graying				
Age	0.861	< 0.001	0.840	0.882
Sex (men)	1.830	0.008	1.169	2.863

DYEING OF GRAY HAIR

Reversal of gray hair

- **Hair repigmetation**
  - partial spontaneous reversal of canaties during the early stage of canaties
  - after radiation therapy for cancer



Shetty M. Br Med J. 1995

- after erythrodermic eczema and erosive candidiasis of the scalp

Vervov J. Br J Dermtol. 1981

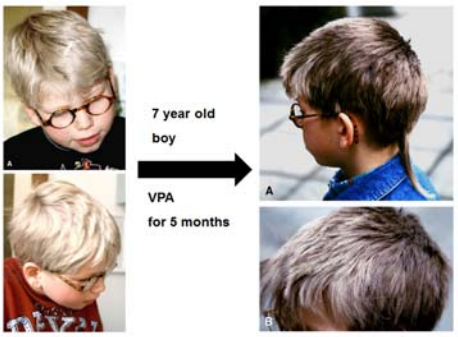
❖ radiation/cytokine-induced activation of upper ORS MCs
→ migrate to and differentiate in the melanogenic zone of the greying HF

Temporary hair darkening by drug

- **P-aminobenzoic acid.**
  - 100 mg three times daily to 460 gray-haired individuals and noted a response in 82%.
  - **Darkening was obvious within 2–4 months** of starting treatment.
  - The hairs turned **gray again 2–4 weeks after stopping therapy**.
  - The mechanism of action has remained unclear.

Sieve et al. 1941

Hair darkening by valproic acid



Dyeing of gray hair

- **In the absence of a natural way to reverse hair graying, hair colorants are the mainstays of recovering lost hair color.**

Ann Dermatol Vol. 25, No. 4, 2013 http://dx.doi.org/10.5021/ad.2013.25.4.401

ORIGINAL ARTICLE

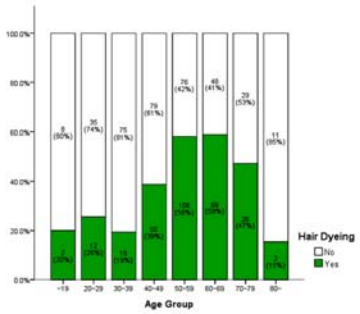
The Pattern of Hair Dyeing in Koreans with Gray Hair

Seong Jin Jo[1,2], Hyoneung Shin[1], Seung Hwan Paik[1], Jae Woo Choi[1], Jong Hee Lee[1,3], Soyun Cho[2,3], Chinsang Kwon[1,3]

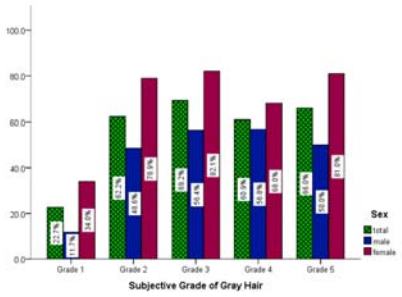
[1]Department of Dermatology, [2]Institute of Dermatological Science, Medical Research Center, Seoul National University College of Medicine, [3]Department of Dermatology, SMG-SNU Boramae Medical Center, Seoul, Korea

- **Behavior pattern of hair dyeing**
  - Age
  - Gender
  - Extent of grayness

Behavior pattern in hair dyeing : by age



Behavior pattern in hair dyeing : by the extent of grayness and gender



Is Premature Hair Graying a Risk Factor of Systemic Diseases?

Diseases associated with premature graying

- **Pernicious anemia**
- **Thyroid disease**
- **Osteopenia**
- **Progeria**
- **Pangeria**
- **Werner synderome**

...

However, people without any severe medical prob lems are much more common.

Is early onset of gray hair a risk factor?

- **195 consecutive office patients over the age of 40**
- **874 autopsy patients**
  - myocardial infarction, congestive heart failure, cancer, stroke, pneumonia/bronchitis, or cirrhosis of the liver
  - no evidence to support the contention that early gray hair is a risk.

Glasser. 1991

- **Copenhagen City Heart Study**
  - 13,000 men and women
  - No correlation between the mortality and the extent of graying of hair

Schnohr et al. 1998

Gray hair associated diseases?

- **Coronary artery diseases**
  - Premature hair graying: a probable coronary risk factor
    Gould et al. 1978
    - **Gray hair in black males a possible risk factor in coronary artery disease**
      Eisenstein et al. 1982
  - Copenhagen City Heart Study
    - 20,000 men and women (> 20 yrs)
    - The relative risk of MI was 1.9 for men with completely gray hair compared with men with no gray hair (p<0.001)
      Schnohr et al. 1995
- **Osteopenia**
  - Subjects with premature graying but no other identifiable risk factor were 4.4 times as likely to have osteopenia as subjects without premature graying (P = 0.02)
    Rosen et al. 1994
  - premature hair graying is associated with low bone density
    Orr-Walker et al. 1997
    Morton et al. 2007

Angiology. 1978 Nov;29(11):800-3.

Premature Hair Graying: A Probable Coronary Risk Factor

Materials and Methods

During the 2 years from July 1974 to July 1976, 50 patients under the age of 50 were admitted to the coronary care unit with a proven diagnosis of a myocardial infarction. Typical serial electrocardiographic changes as well as elevations of the SGOT, CPK, and LDH were present in these patients.

Questionnaries were completed at the time of admission to determine the presence or absence of hypertension, diabetes, smoking habits, and lipid abnormalities. In addition, the color of the hair was evaluated. If the patient was prematurely totally gray, the age of onset of the graying was ascertained.

Results

There were 50 patients. Thirty-eight did not have premature graying. Twelve of the male patients (24%) had virtual total graying of the hair which made them appear older than their stated age. The graying in these patients started on the average at 29 years. Five of these patients state that other family members had premature hair graying. The incidence of diabetes, hypertension, and smoking was similar in those with and without premature hair graying.

Am Heart J. 1995 Nov;130(5):1003-10.

Gray hair, baldness, and wrinkles in relation to myocardial infarction: The Copenhagen City Heart Study

The Copenhagen City Heart Study

A prospective cardiovascular population study comprising a random sample of 20,000 men and women aged > 20 years. 7163 (75% of those invited) women and 5837 (69%) men fulfilled the criteria for inclusion

Subjects

During the 12-year follow-up, **750 cases of first-time MI** were observed.

Table II. The distribution by sex and age of 750 first-time myocardial infarctions in the study population during 12 years of follow-up

	Women		Men	
Age (yr)	Participants	MI	Participants	MI
20-39	799	6	732	12
40-49	1678	14	1418	72
50-59	2745	78	1918	186
60-69	1591	89	1430	206
70-79	350	37	341	46
Total	7163	226	5837	524

Results

A correlation between graying of the hair, facial wrinkling, and frontoparietal baldness and crown-top baldness and MI in men.

With regard to gray hair, a similar although weaker and not statistically significant trend was seen in women.

We conclude that, in addition to established coronary risk factors, aging signs like graying of the hair, male baldness, and facial wrinkling indicate an additional risk of MI.

Table XIII. RR of first time myocardial infarction with regard to aging variables in subjects younger than 55 years of age

	Men			Women		
Variable	RR	95% Confidence limits	p Value	RR	95% Confidence limits	p Value
Wrinkles						
no/few	1.0			1.0		
severe	1.6	(1.1-2.3)	0.05	1.3	(0.9-1.8)	NS
Gray hair						
No	1.0			1.0		
Moderately	1.4	(0.9-2.3)	NS	1.0	(0.6-1.5)	NS
Totally	1.6	(1.1-3.3)	0.05	1.4	(0.9-2.1)	NS
Baldness Frontoparietal						
No baldness	1.0			1.0		
Bald triangle	1.6	(0.9-2.9)	NS	1.3	(0.8-2.0)	NS
Crown top						
No baldness	1.0					
Bald spot	1.2	(0.8-1.8)	NS			
Combined						
No baldness	1.0					
Bald spot	1.6	(1.1-2.6)	0.05			

J Gerontol A Biol Sci Med Sci. 1998 Sep;53(5):M347-50.

Longevity and Gray Hair, Baldness, Facial Wrinkles, and Arcus Senilis in 13,000 Men and Women: The Copenhagen City Heart Study

METHODS

During 16 years of follow-up, 3,939 persons (1,656 women and 2,283 men) had died..

RESULTS

No correlation between the mortality and the extent of graying of the hair, or baldness or facial wrinkles in either of the sexes, irrespective of age.

Men with no gray hair had a slightly, but significantly, lower mortality than the rest [relative risk (RR) = .81, 95% confidence interval (CI) .67-.98; p < .05].

CONCLUSION

We conclude that the degrees of graying of the hair, baldness, and facial wrinkles are not predictive of a shorter life span in men and women in the Copenhagen City Heart Study.

Table 2. Percentage of Deaths During 16 Years According to Graying of the Hair by Sex and Age*

Age Group (years)	No Gray Hair	Few Gray Hairs	Moderate Gray Hairs	Completely Gray/ White Hairs
Women				
30–39	4.9	4.8	—	—
40–49	10	10	8.1	7.8
50–59	17	22	20	21
60–69	30	39	41	41
70–79	—	69	64	72
Men				
30–39	6.1	6.8	—	—
40–49	13	18	17	18
50–59	30	37	34	38
60–69	56	63	61	62
70–79	—	81	85	85

*(— means < 20 persons in category).

Intern Med 52: 29-36, 2013 DOI: 10.2169/internalmedicine.52.7842

Premature Hair Whitening is an Independent Predictor of Carotid Intima-media Thickness in Young and Middle-aged Men

Methods

Young and middle-aged patients (<55 years age) without a history of CVD

202 eligible patients admitting to the outpatient clinic for CVRF management

A gray/white-hair scale was used to determine the percentage of hair whitening.

Assessing carotid intima-media thickness (CIMT) using B-mode SONO.

The Gray/white Hair Scale

Gray Hair Stages						
No gray hair	First scarce gray hair	<5%	Trace	5-25%	Diffuse gray hair	25-50%
0%	Generalized gray hair	50-75%	From gray to white	75-100%	Generalized white hair	100%
	Moderate		Manifest		Complete	

Gray/white hair percentage (0 to 100%): .....

Parameters n (202)	CIMT < 0.9mm (124)	CIMT ≥ 0.9mm (78)	p value
Age (yrs)	41±6	47±4	<0.001
BMI (kg/m^2)	28.2±3.4	30.2±4.3	<0.001
Waist circumference (cm)	97.6±9.8	107.3±12.2	<0.001
Hypertension	15%	37%	<0.001
Diabetes mellitus	5%	18%	0.002
Smoking	55%	68%	0.064
Hyperlipidemia	36%	49%	0.080
Family history of CAD	19%	37%	0.003
FPG (mg/dL)	101±38	110±45	NS
Creatinine (mg/dL)	0.89±0.12	0.88±0.11	NS
Uric Acid (mg/dL)	5.3±1.1	6.1±1.4	<0.001
Total cholesterol (mg/dL)	203±41	216±45	0.045
LDL (mg/dL)	123±35	140±37	0.003
HDL (mg/dL)	43±12	41±7	NS
Triglyceride (mg/dL)	191±148	187±122	NS
Leukocytes (/mm^3)	7,671±1,668	7,964±1,651	NS
Hemoglobin (mg/dL)	15±1.0	15±1.2	NS
Platelets (10^3 /mm^3)	274±54	273±52	NS
CRP (mg/dL)	0.36±0.44	0.63±0.70	0.009
Total bilirubin (mg/dL)	0.90±0.47	0.65±0.28	<0.001
Indirect bilirubin (mg/dL)	0.59±0.36	0.42±0.21	<0.001
Direct bilirubin (mg/dL)	0.31±0.13	0.23±0.09	<0.001
GGT (U/L)	31±15	41±29	0.006
Onset age of HW (yrs)	27±10	30±7	NS
Percentage of white hairs	32±34	78±28	<0.001
Family history of early hair whitening	14%	22%	NS
Percentage of hair loss	12±16	14±16	NS
Ejection fraction (EF %)	65±5	64±4	NS

Table 2. Baseline Characteristics of the Study Population in the Groups Determined according to HWS

n (202)	Categories of the hair whitening (HW)					
HW Scores n	Trace (63)	Mild (18)	Moderate (45)	Manifest-Overt (47)	Complete (29)	p value
Age (yrs)	41±5	43±6	42±6	44±6	49±5	<0.001
BMI (kg/m^2)	28.6±3.3	29.2±3.1	28.1±4.5	29.6±3.8	30.2±4.5	NS
Waist circumference (cm)	98±10	100±10	100±14	106±11	106±13	0.011
Hypertension	11%	22%	18%	38%	41%	0.003
Diabetes Mellitus	5%	6%	9%	19%	10%	NS
Smoking	54%	50%	60%	60%	76%	NS
Family history of CAD	15%	17%	36%	31%	26%	NS
Hyperlipidemia	43%	28%	44%	42%	41%	NS
FPG (mg/dL)	99.5±28.1	112.6±79.6	95.8±13.1	117.6±57.3	102.2±19.1	NS
Creatinine (mg/dL)	0.90±0.13	0.90±0.10	0.90±0.12	0.88±0.12	0.89±0.11	NS
Uric acid (mg/dL)	5.3±1.1	5.3±1.4	5.4±1.0	5.8±1.3	6.3±1.5	0.008
Total cholesterol (mg/dL)	208±45	206±42	205±38	213±45	209±43	NS
LDL (mg/dL)	131±41	122±25	127±33	131±40	135±33	NS
HDL (mg/dL)	42±9	42±7	42±9	43±15	41±6	NS
Triglycerides (mg/dL)	180±106	194±157	199±142	203±191	171±75	NS
Total bilirubin (mg/dL)	0.91±0.49	1.28±0.65	0.70±0.27	0.67±0.28	0.68±0.28	<0.001
Indirect bilirubin (mg/dL)	0.60±0.38	0.86±0.53	0.45±0.21	0.42±0.20	0.43±0.20	<0.001
Direct bilirubin (mg/dL)	0.30±0.13	0.42±0.19	0.24±0.09	0.25±0.11	0.25±0.09	<0.001
GGT (U/L)	32±14	28±13	37±30	38±25	34±22	NS
Leukocytes (10^3/mm^3)	7.6±1.6	8.0±1.5	7.8±1.8	7.8±1.8	7.9±1.5	NS
Platelets (10^3/mm^3)	275±48	303±46	274±54	264±57	269±58	NS
Hemoglobin (mg/dL)	15±1.0	16±0.8	15±1.1	15±1.3	15±1.1	NS
CRP (mg/dL)	0.25±0.16	0.28±0.14	0.51±0.60	0.79±0.94	0.54±0.46	0.002
Ejection fraction (EF %)	64±4	66±4	65±3	64±5	64±4	NS
Right CIMT (mm)	0.69±0.10	0.74±0.10	0.84±0.12	0.92±0.13	0.94±0.12	<0.001
Left CIMT (mm)	0.69±0.10	0.75±0.08	0.84±0.11	0.92±0.12	0.96±0.13	<0.001
Mean CIMT (mm)	0.69±0.10	0.74±0.09	0.84±0.11	0.92±0.12	0.95±0.12	<0.001
Plaque	2%	0%	11%	30%	41%	<0.001

CAD: coronary artery disease, GGT: gamma-glutamyltransferase, HWS: hair whitening score, BMI: body mass index, FPG: fasting plasma glucose, CRP: C-reactive protein, CIMT: carotid artery intima media thickness, HDL: high-density lipoprotein, LDL: low-density lipoprotein

J Clin Endocrinol Metab. 1994 Sep;79(3):854-7.

Premature graying of hair is a risk marker for osteopenia

the association between premature graying of hair and osteopenia (lumbar bone density t score, below -1.0).

Premature graying of hair in **36** men and women with osteopenia (cases) was compared to that in **27** men and women without osteopenia (controls).

Subjects with premature graying but no other identifiable risk factor were 4.4 times as likely to have osteopenia as subjects without premature graying (P = 0.02).

a stronger family history of osteoporosis

J Clin Endocrinol Metab. 1997 Nov;82(11):3580-3.

Premature Hair Graying and Bone Mineral Density*

BRANDON J. ORR-WALKER, MARGARET C. EVANS, RUTH W. AMES, JUDITH M. CLEARWATER, AND IAN R. REID

Subjects & Methods

404 normal postmenopausal women
A written questionnaire

Results

293 healthy postmenopausal women
Subjects experiencing onset of hair graying in their 20s tended to have lower bone mineral density throughout the skeleton (adjusted for age and weight).
The same was true for those in whom the majority of their hair was gray by the age of 40 yr (n = 16).
Bone density at the lumbar spine and Ward's triangle showed similar trends that were not significant.
However, premature hair graying explained only 0.6-1.3% of the variance in bone mineral density within the population.

Conclusion

Premature hair graying is associated with low bone density, but its infrequency in the normal postmenopausal population leads to its accounting for only a tiny fraction of the variance of bone density.

J Aging Health. 2007 Apr;19(2):275-85.

Premature Graying, Balding, and Low Bone Mineral Density in Older Women and Men: The Rancho Bernardo Study

Subjects

Between 1972 and 1974, 82% of adult residents of Rancho Bernardo (a community in southern California) participated in a survey of heart disease risk factors. This cohort has been followed with annual mailed questionnaires and periodic clinic visits.

The 1,207 participants (n=717 women, and n=490 men) aged 50 and older at the 1992-1996 clinic visit are the focus of this report

Procedures

They were considered to be "prematurely gray" if they indicated that all or most of their hair was gray before they were 40 years of age.

Results

Graying was not significantly associated with BMD in men or women.

Balding men averaged 5% lower total body BMD ($p \leq 0.05$), and balding women had ~24% higher mean hip BMD ($p \leq 0.05$).

Graying and balding women reported a higher proportion of current estrogen use; balding women reported more use of glucocorticosteroids.

Balding women currently using estrogen may explain the higher BMD.

BMJ. 1996 Dec 21-28;313(7072):1616.

Premature grey hair and hair loss among smokers: a new opportunity for health education?

All new patients attending a general surgical outpatient clinic were studied over three months. There were 606 patients aged over 30 years.

Of the 268 men and 338 women, 152 of each sex smoked.

The overall odds ratio for the relation of grey hair and smoking was then calculated, for both men and women, excluding bald subjects, allowing for the relation between grey hair colour and age, giving a value of 4.40 (3.24 to 5.96).

Table 1—*Numbers of smokers and non-smokers with natural, grey, or balding hair according to age and sex*

Hair colour or loss	Men				Women				Total (No (%))
	≤40	41-50	51-60	>60	≤40	41-50	51-60	>60	
Smokers									
Natural	8	4	0	0	10	13	1	0	36 (12)
Grey	3	11	11	12	13	54	22	37	163 (54)
Bald	2	30	22	49	0	1	0	1	105 (35)
Subtotal	13	45	33	61	23	68	23	38	304 (100)
Non-smokers									
Natural	2	13	3	0	30	21	23	4	96 (32)
Grey	0	7	14	12	0	27	47	36	143 (47)
Bald	6	12	9	34	2	0	0	0	63 (21)
Subtotal	8	32	26	46	32	48	70	40	302 (100)
Total	21	77	59	107	55	116	93	78	606

Indian Dermatol Online J. 2013 Apr;4(2):90-2.

Smokers' hair: Does smoking cause premature hair graying?

Materials and Methods

A cross-sectional observational study
207 participants (94 men and 113 women, Jordanian people)
PHG was defined as the first appearance of gray hair before the age of 30.

Results

The prevalence of smokers in the "PHG" group was higher (40.2% vs. 24.7%, P = 0.031). Smokers had earlier onset of hair graying (smokers: 31 (7.4) vs. nonsmokers: 34 (8.6), P = 0.034).

Using multiple logistic regression with conditional likelihood, smokers were two and half times (95% CI: 1.5-4.6) more prone to develop PHG.

Table 1: Clinical characteristics of participants by the onset of first appearance of gray hair

Variable	Premature hair gray (N=104) mean±SD or N (%)	Normal hair gray (N=103) mean±SD or N (%)	P value
Age (years)	40.5±12.8	52.9±11.9	<0.000
Height (m)	1.67±0.09	1.65±0.09	0.11
Weight (kg)	78.8±15	78±15.3	0.73
BMI (kg/m²)	28.9±5.3	28.1±5.3	0.3
Waist circumference (cm)	95.6±14.4	96.5±12.6	0.67
Fasting blood glucose (mg/dl)	104.3±26.8	108.5±25.9	0.29
Diabetes	6 (5.8)	12 (11.7)	0.13
Systolic blood pressure (mmHg)	121.6±11.3	123.7±16.7	0.32
Diastolic blood pressure (mmHg)	80.1±7.5	82±8.2	0.11
Hypertension	8 (7.7)	29 (28.2)	<0.001

Arch Dermatol. 2007 Jan;143(1):116-8.

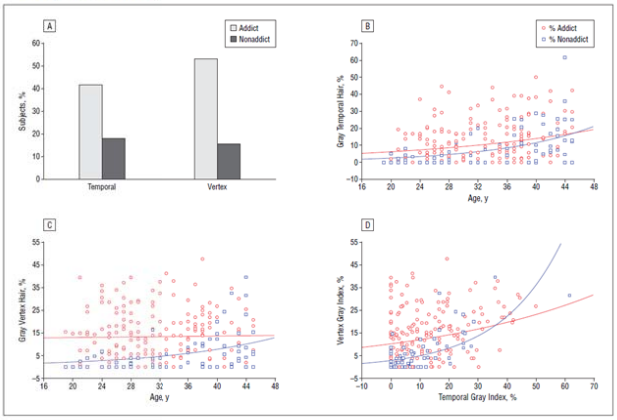
Hair Graying in Substance Addiction

Table. Sociodemographic and Drug Use Profile*

Characteristic	Addicts	Nonaddicts
Age range, y	19-45	20-45
Sample size, No.	197	79
Age, y	31.51 (6.47)	33.47 (8.70)
Men, %	77.00	59.20
Race, %		
Asian-Australian	8.20	0.65†
ATSI	4.10	10.20
White	87.70	89.15
Drug use		
Cigarettes, No.	16.63 (10.97)	3.88 (7.81)†
Smoking duration, y	14.72 (8.62)	4.22 (9.51)†
Alcohol dose, g/d	9.52 (18.47)	0.00†
Drinking duration, y	2.49 (4.75)	0.00†
Cannabis dose, g/d	2.96 (5.62)	0.33 (1.0)†
Cannabis use duration, y	6.87 (7.02)	0.56 (1.66)†
Heroin dose, g/d	0.56 (1.09)	0.00†
Heroin use duration, y	9.44 (6.70)	0.00†
Morphine dose, g/d	0.05 (0.24)	0.00†
Morphine use duration, y	1.71 (5.22)	0.00†
Methadone dose, maximum, mg/d	34.53 (50.17)	0.00†
Methadone use duration, y	1.22 (2.49)	0.00†
Amphetamine dose, g/d	0.48 (1.82)	0.00†
Amphetamine use duration, y	1.89 (5.28)	0.00†

Abbreviation: ATSI, Aboriginal and Torres Strait Islander.
*Unless otherwise indicated, data are reported as mean (SD) values.
†P<.001.

Hair graying in subjects younger than 45 years



Biol Trace Elem Res (2012) 146:30–34

Serum Iron, Zinc, and Copper Concentration in Premature Graying of Hair

Subjects

patients under 20 years old , having a minimum of ten gray hair fibers
66 patients and 66 sex–age-matched controls

Results

The mean age of studied cases was 17.8±2.0 years.
The mean age of the onset of canities was 15.5±3.2 years.

Table 1 Comparison of demographic characteristic and serum mineral concentrations between the two groups

	Case, n=66	Control, n=66	P
Age, years	17.8±2.0	18.3±1.5	0.58
Female/male	45/21	45/21	–
Positive family history	43.9%	28.8%	0.07
Zn (μg/dL)	114.8±67.8	108.2±49.9	0.285
Cu (μg/dL)	90.7±37.4 <	105.3±50.2	0.048
Fe (μg/dL)	108.3±48.4 >	88.8±39.5	0.0085

Int J Trichology. 2013 Jan;5(1):17-21.

Epidemiological and Investigative Study of Premature Graying of Hair in Higher Secondary and Pre-University School Children

Materials and Methods

A total of 35 cases and 35 age and sex matched controls
Students of less than 20 years of age
Premature graying of hair: a minimum of 5 gray hair fibers in a person less than 20 years of age

Results

Serum Ca, Serum Ferritin and vitamin D3 were low in patients with premature graying of hair
Controversial to Naieni et al.

Table 1: Comparision of Hb, TIBC, S. Iron, S. Ferritin, S. Ca and Vitamin B12 in cases and controls

Cases	Cases	Controls	Level of significance
Hb (g/dl)	12.93±1.74	13.43±1.42	0.196 (NS)
TIBC (mg/dl)	363.60±50.18	356.51±341	0.623 (NS)
S. Iron (mg/dl)	74.62±32.91	84.94±30.26	0.142 (NS)
S. Ferritin (mcg/l)	36.88±35.11	60.93±53.08	0.03 (Sig)
S. Ca (mg/dl)	9.47±0.31	9.71±0.50	0.018 (Sig)
vitamin B12 (pg/ml)	479.70±214.82	458.37±265.19	0.466 (NS)

Hb – Hemoglobin; TIBC – Total iron binding capacity; S. Ferritin – Serum ferritin; S.Ca – Serum calcium; S. Iron – Serum iron; NS – Not significant; Sig – Significant

Table 2: Vitamin D3 levels in cases and controls

vitamin D3 levels	Cases (%)	Controls (%)
Deficient	16 (45.7)	7 (20)
Insufficient	19 (54.3)	16 (45. 7)
Normal	0 (0)	12 (34.3)

χ^2=15.779, P<0.001 h; HS – Highly significant

Association of premature hair graying with family history, smoking, and obesity: A cross-sectional study

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Background: Many researchers have been concerned about the association of hair graying with systemic diseases. However, the common factors associated with hair graying and systemic diseases have not been elucidated.

Objective: This study aimed to identify risk factors for premature hair graying (PHG) in young men.

Methods: We conducted a cross-sectional study using questionnaires in young men. After a pilot study that included 1069 men, we surveyed 6390 men younger than 30 years about their gray hair status and various socioclinical characteristics.

Results: The age of participants in the main survey was 20.2 ± 1.3 years (mean ± SD). Of the 6390 participants, 1618 (25.3%) presented with PHG. Family history of PHG (odds ratio [OR], 12.82), obesity (OR, 2.61), and >5 pack-years history of smoking (OR, 1.61) were significantly associated with PHG. In the multivariate analysis, family history of PHG (OR, 2.63) and obesity (OR, 2.22) correlated with the severity of PHG.

Limitations: Owing to the use of questionnaires, the possibility of recall bias exists. Women were not evaluated in this study.

Conclusion: Smoking, family history of PHG, and obesity are important factors associated with PHG. (J Am Acad Dermatol 2015;72:321-7.)

Key words: body mass index; gray hair; obesity; premature hair graying; smoking.

Socio-clinical characteristics and comparison between respondents with and without PHG

Socio-clinical characteristics	Total	non-PHG	PHG	Statistical method	OR (95% CI)	*P*-value
Number of subjects	6390	4772	1618			
Age, years (mean ± SD)	20.2 ± 1.3	20.2 ±1.3	20.3±1.5	Binary logistic regression analysis	1.07 (1.03 - 1.11)	0.002
Obesity categories[a], n (%)	6232 (100.0)	4654 (100.0)	1578 (100.0)	Binary logistic regression analysis		
underweight	520 (8.3)	394 (8.5)	126 (8.0)		1.03 (0.83 - 1.28)	0.774
normal	4188 (67.2)	3197 (68.7)	991 (62.8)		1.00 [Reference]	_
overweight	1159 (18.6)	834 (17.9)	325 (20.6)		1.26 (1.09 - 1.46)	0.002
obese	365 (5.9)	229 (4.9)	136 (8.6)		1.92 (1.53 - 2.40)	< 0.001
Family history of PHG, n (%)	6390 (100.0)	4772 (100.0)	1618 (100.0)	Chi-square test	_	< 0.001
no	2603 (40.7)	2356 (49.4)	247 (15.3)	Binary logistic regression analysis	1.00 [Reference]	_
yes	668 (10.5)	303 (6.3)	365 (22.5)		11.49 (9.40 - 14.05)	< 0.001
unknowingness	3119 (48.8)	2113 (44.3)	1006 (62.2)		_	_
Scalp skin disease, n (%)	6250 (100.0)	4673 (100.0)	1577 (100.0)	Binary logistic regression analysis		
normal	5982 (95.7)	4489 (96.1)	1493 (94.7)		1.00 [Reference]	_
seborrheic dermatitis	202 (3.2)	137 (2.9)	65 (4.1)		1.43 (1.06 - 1.93)	0.021
other scalp disease	66 (1.1)	47 (1.0)	19 (1.2)		1.22 (0.71 - 2.08)	0.476
Medical history of admission or operation, n (%)	6247 (100.0)	4672 (100.0)	1575 (100.0)	Chi-square test	_	0.880

Medical history of admission or operation, n (%)	6247 (100.0)	4672 (100.0)	1575 (100.0)	Chi-square test	_	0.880
no	3901 (62.4)	2920 (62.5)	981 (62.3)	Binary logistic regression analysis	1.00 [Reference]	_
yes	2346 (37.6)	1752 (37.5)	594 (37.7)		1.01 (0.90 - 1.14)	0.879
Chronic disease, n (%)	6244 (100.0)	4669 (100.0)	1575 (100.0)	Chi-square test	_	0.648
no	5805 (93.0)	4345 (93.1)	1460 (92.7)	Binary logistic regression analysis	1.00 [Reference]	_
yes	439 (7.0)	324 (6.9)	115 (7.3)		1.06 (0.85 - 1.32)	0.648
Androgenetic alopecia, n (%)	6021 (100.0)	4493 (100.0)	1528 (100.0)	Chi-square test	_	0.124
no	5893 (97.9)	4405 (98.0)	1488 (97.4)	Binary logistic regression analysis	1.00 [Reference]	_
yes	128 (2.1)	88 (2.0)	40 (2.6)		1.35 (0.92 - 1.96)	0.124
Medication, n (%)	6134 (100.0)	4574 (100.0)	1560 (100.0)	Chi-square test	_	0.249
no	5793 (94.4)	4329 (94.6)	1464 (93.8)	Binary logistic regression analysis	1.00 [Reference]	_
yes	341 (5.6)	245 (5.4)	96 (6.2)		1.16 (0.91 - 1.48)	0.236
Smoking[b], n (%)	6176 (100.0)	4630 (100.0)	1546 (100.0)	Chi-square test	_	0.014
no	5348 (86.6)	4038 (87.2)	1310 (84.7)	Binary logistic regression analysis	1.00 [Reference]	_
yes	828 (13.4)	592 (12.8)	236 (15.3)		1.23 (1.04 - 1.45)	0.013
Alcohol, n (%)	6357 (100.0)	4753 (100.0)	1604 (100.0)	Cochran-Armitage trend test	_	0.210
No	648 (10.2)	496 (10.4)	152 (9.5)	Binary logistic regression analysis	1.00 [Reference]	_
≤ 1/month	855 (13.4)	649 (13.7)	206 (12.8)		1.04 (0.82 - 1.32)	0.774
2 - 3/month	2000 (31.5)	1467 (30.9)	533 (33.2)		1.19 (0.96 - 1.46)	0.107
1 - 2/week	1990 (31.3)	1506 (31.7)	484 (30.2)		1.05 (0.85 - 1.29)	0.655
≥ 3/week	864 (13.6)	635 (13.4)	229 (14.3)		1.18 (0.93 - 1.49)	0.177
Exercise, n (%)	6334 (100.0)	4737 (100.0)	1597 (100.0)	Cochran-Armitage trend test	_	0.060
No	1301 (20.5)	954 (20.1)	347 (21.7)	Binary logistic regression analysis	1.00 [Reference]	_
≤ 1/month	1036 (16.4)	761 (16.1)	275 (17.2)		0.99 (0.83 - 1.20)	0.993
2 - 3/month	1799 (28.4)	1352 (28.5)	447 (28.0)		0.91 (0.77 - 1.07)	0.909
1 - 2/week	1454 (23.0)	1108 (23.4)	346 (21.7)		0.86 (0.72 - 1.02)	0.859
≥ 3/week	744 (11.7)	562 (11.9)	182 (11.4)		0.89 (0.72 - 1.10)	0.890
Diet, n (%)	6263 (100.0)	4686 (100.0)	1577 (100.0)	Binary logistic regression analysis		
Vegetarian diet	111 (1.8)	91 (1.9)	20 (1.3)		0.67 (0.41 - 1.09)	0.109
Mixed diet	3982 (63.6)	2999 (64.0)	983 (62.3)		1.00 [Reference]	_
Meat based diet	2170 (34.6)	1596 (34.1)	574 (36.4)		1.10 (0.97 - 1.24)	0.128
Educational background, n (%)	6193 (100.0)	1559 (100.0)	4634 (100.0)	Cochran-Armitage trend test	_	0.740
Middle school graduation	136 (2.2)	33 (2.1)	103 (2.2)	Binary logistic regression analysis	0.96 (0.65 - 1.43)	0.845
High school graduation	1945 (31.4)	498 (31.9)	1447 (31.2)		1.03 (0.91 - 1.17)	0.613
College student or graduation	4112 (66.4)	1028 (65.9)	3084 (66.6)		1.00 [Reference]	_
Scholarly achievement, n (%)	6055 (100.0)	4516 (100.0)	1539 (100.0)	Binary logistic regression analysis		

90 - 100 %	243 (4.0)	167 (3.7)	76 (3.05)		1.29 (0.97 - 1.70)	0.081
70 - 90 %	1291 (21.3)	985 (21.8)	306 (19.9)		0.88 (0.76 - 1.02)	0.086
30 - 70 %	3353 (55.4)	2476 (54.8)	877 (57.0)		1.00 [Reference]	_
10 - 30 %	897 (14.8)	685 (15.2)	212 (13.8)		0.87 (0.74 - 1.04)	0.125
0 - 10 %	271 (4.5)	203 (4.5)	68 (4.4)		0.95 (0.71 - 1.26)	0.701
Occupation, n (%)	4964 (100.0)	3687 (100.0)	1277 (100.0)	Binary logistic regression analysis		
student	4197 (84.5)	3145 (85.3)	1052 (82.4)		1.00 [Reference]	_
white-collar worker	133 (2.7)	93 (2.5)	40 (3.1)		1.29 (0.88 - 1.88)	0.191
blue-collar worker	84 (1.7)	53 (1.4)	31 (2.4)		1.75 (1.12 - 2.74)	0.015
service industry worker	521 (12.4)	378 (10.3)	143 (11.2)		1.13 (0.92 - 1.39)	0.239
self-employed	29 (0.6)	18 (0.5)	11 (0.9)		1.83 (0.86-3.89)	0.117
Stress Severity Scale (BEPSI-K), n (%)	6296 (100.0)	4702 (100.0)	1594 (100.0)	Binary logistic regression analysis		
mild	3875 (61.5)	3005 (63.9)	872 (54.7)		1.00 [Reference]	_
moderate	2012 (32.0)	1423 (30.3)	589 (37.0)		1.43 (1.26 - 1.61)	< 0.001
severe	407 (6.5)	274 (5.8)	133 (8.3)		1.67 (1.34 - 2.09)	< 0.001
Fitzpatrick skin type, n (%)	6295 (100.0)	4707 (100.0)	1588 (100.0)	Cochran-Armitage trend test	_	0.050
type I	427 (6.8)	316 (6.7)	111 (7.0)	Binary logistic regression analysis	1.00 [Reference]	_
type II	1237 (19.7)	906 (19.2)	331 (20.8)		1.04 (0.81 - 1.34)	0.758
type III	1802 (28.6)	1349 (28.7)	453 (28.5)		0.96 (0.75 - 1.22)	0.714
type IV	1892 (30.1)	1415 (30.1)	477 (30.0)		0.96 (0.76 - 1.22)	0.737
type V	816 (13.0)	619 (13.2)	197 (12.4)		0.91 (0.69 - 1.19)	0.472
type VI	121 (1.9)	102 (2.2)	19 (1.2)		0.53 (0.31 - 0.91)	0.020

Socio-clinical factors associated with the development of PHG using multivariate logistic regression analyses

Socio-clinical characteristics	OR (95% CI)	*P*-value
Family history of PHG	12.82 (9.94 - 16.55)	< 0.001
Obesity categories[a]		
Underweight	0.61 (0.37 - 1.03)	0.064
Normal	1.00 [Reference]	
Overweight	1.28 (0.94 - 1.74)	0.122
Obese	2.61 (1.62 - 4.23)	< 0.001
Smoking[b]	1.61 (1.10 - 2.37)	0.014

OR; odds ratios

CI; confidence intervals

[a] World Health Organization (WHO) criteria

[b] Smoking more than 5 pack-years

Socio-clinical factors associated with the severity of PHG using multivariate ordinal logistic regression analysis

Socio-clinical characteristics	Number of white hair, n (%)			OR (95% CI)	*P*-value
	≤ 10	10 - 100	≥ 100		
Family history of PHG					
no	171 (69.2)	58 (23.5)	18 (7.3)	1.00 [Reference]	
yes	167 (45.8)	148 (40.5)	50 (13.7)	2.63 (1.88 - 3.69)	< 0.001
Obesity categories[a]					
underweight	83 (65.9)	36 (28.6)	7 (5.6)	0.89 (0.46 - 1.73)	0.726
normal	628 (63.4)	307 (31.0)	56 (5.7)	1.00 [Reference]	
overweight	182 (56.0)	123 (37.8)	20 (6.2)	1.35 (0.91 - 2.01)	0.136
obese	69 (50.7)	54 (39.7)	13 (9.6)	2.22 (1.30 - 3.79)	0.004

OR; odds ratios

CI; confidence intervals

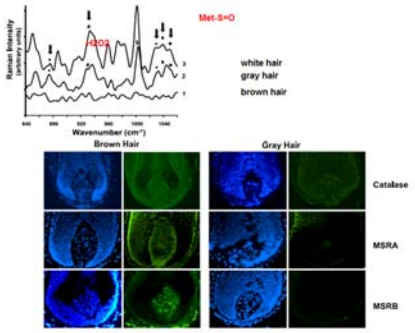
[a] World Health Organization (WHO) criteria

Factors Associated with Premature Hair Graying

Free radical theory of graying

Arck PC et al. 2006

Oxidative stress



Wood J. 2009

Take Home Message

- **Decrease in number of melanocytes**
- **Onset of hair-graying: 40s in Koreans**
- **Gender difference in hair graying pattern**
- **Risk factors of Hair graying**
  - Age
  - Sex
  - Family history
  - Smoking
  - Obesity
- **Premature Hair Graying might be associated with systemic medical condition.**

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Hair pigmentation: Basic biological aspects of follicular melanocyte

연세대학교 의과대학 피부과학교실

김 도 영

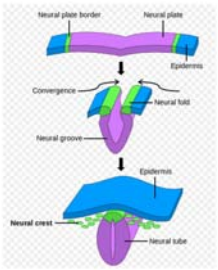
Hair pigmentation:
Basic biological aspects of follicular melanocyte

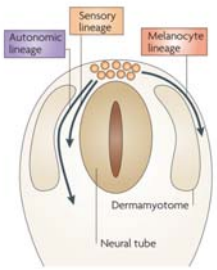
김도영
연세의대 피부과학교실

Contents

- Origin of hair follicle(HF) melanocytes
- MC subpopulations and hair pigmentation
- Melanocyte stem cell (MelSC)
- Aging related hair greying

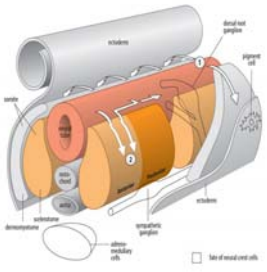
Development of neural crest cells





https://en.wikipedia.org/wiki/Neural_crest

Migration of neural crest cells

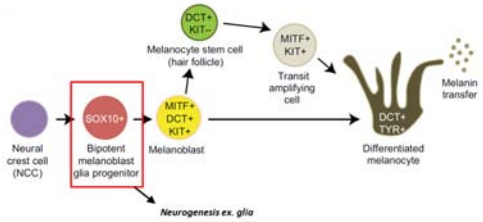


Subtypes of NCC

- *Cranial*
- *Cardiac*
- *Vagal*
- *Trunk: MC origin*

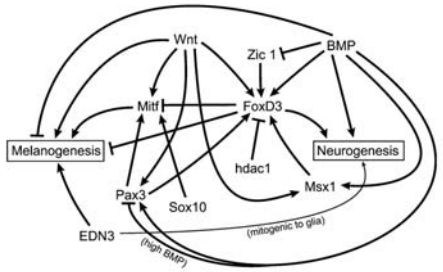
http://www.mun.ca/biology

MC developments in mammals



Mort R. Development 2015;142:620-632

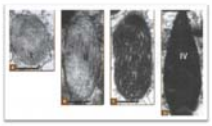
Signaling molecules associated with MC development



Thomas AJ. Pigment Cell Melanoma Res. 2008;21:598-610

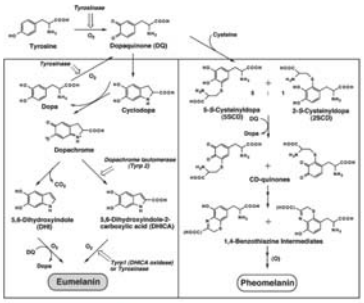
Melanogenesis–melanosome biogenesis

- Two types of melanosome
  - Eumelanosme
  - Pheomelanosome
- Four maturation stages
  - Stage I: premelanosomes develop from the endoplasmic reticulum
  - Stage II: organized, structured fibrillar matrix, but no active melanin synthesis
  - Stage III: deposition of melanin on the fibrillar matrix is found in stage III eumelanosomes
  - Stage IV: fully melanized and matrix is masked by melanin deposits



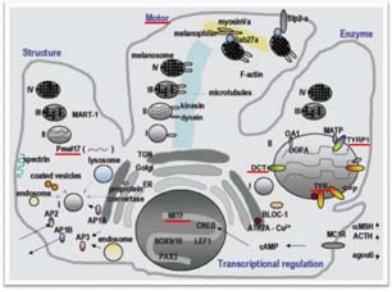
Simon JD. Pigment Cell Melanoma Res. 2009;22(5):563-79.

Melanogenesis–melanin biosynthesis



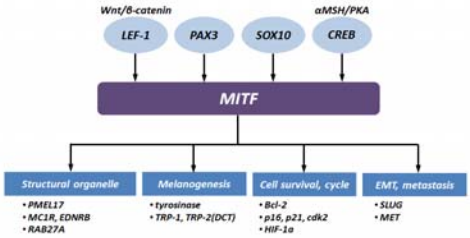
Simon JD. Pigment Cell Melanoma Res. 2009;22(5):563-79.

Factors that affect melanosome biogenesis



Yamaguchi Y. Biofactors 2009;35:193-9

MITF: master transcriptional regulator



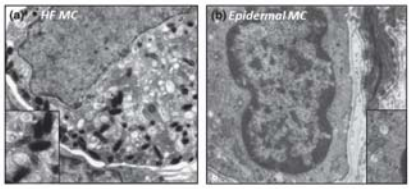
Adapted from Exp Dermatol 2010;19(7):617-27; Hou L. Proc Natl Acad Sci U S A. 2006;13:103

Two main differentiated MCs in skin

Characteristics	Epidermal MC	Follicular MC
Cell morphology	Smaller, less dendritic	Larger, more dendritic
Micro-organelle	Lesser Golgi and rER	More extensive Golgi and rER
Melanosome	Smaller melanosome	Larger melanosome
Fate of melanin	Completely degraded in S. corneum	Retention in hair cortex (similar pigmentation in proximal and distal hair shaft)
Melanogenesis activity cycle	Continuously active (Constitutive)	Coupled with HF cycle (Anagen III-VI)
Preferentially damaged condition	Vitiligo	Acute alopecia areata

Tobin DJ. Int J Cosmet Sci 2008;30(4):233-57

More 'pooled' melanosomes in HF MC

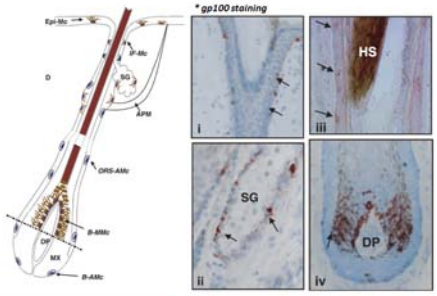


Tobin DJ. Int J Cosmet Sci 2008;30(4):233-57

Localization of HF MCs

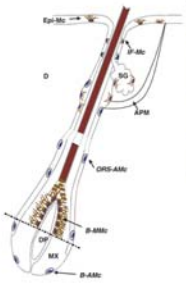
- Differentiated MCs
  - Hair bulb
  - Infundibulum
  - Basal layer of sebaceous gland
- Undifferentiated/not fully differentiated MCs
  - Bulge and mid ORS
  - Proximal hair bulb

MC subpopulation in anagen HF



Tobin DJ. Int J Cosmet Sci 2008;30(4):233-57

MC subpopulation in anagen HF

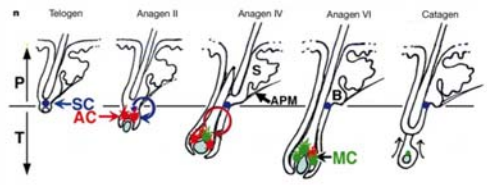


MC subpopulations	Marker (mouse model) *
A-MC in bulge	DCT+ TRP1-, KIT-, tyrosinase-
A-MC in ORS	DCT+, KIT+ TRP1-, tyrosinase-
M-MC in bulb	DCT+, KIT+, TRP1+, tyrosinase+

* Species specific difference, i.e. DCT in undetectable in melanogenic MC of human anagen HF

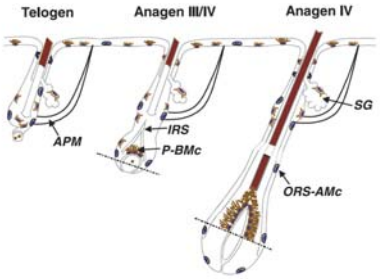
Tobin DJ. Int J Cosmet Sci 2008;30(4):233-57

MC compartments during hair cycle



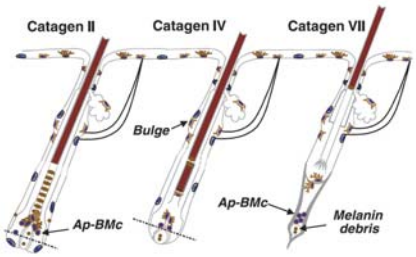
Nishimura E. Nature 2002;416:856-860

MC subsets during hair cycle (1)



Tobin DJ. Int J Cosmet Sci 2008;30(4):233-57

MC subsets during hair cycle (2)

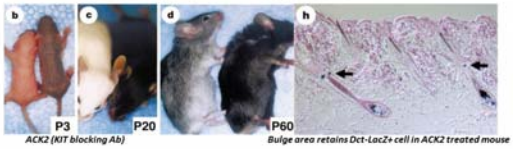


* Hair pigmentation occurs only during anagen and stops very early in the anagen-catagen transition

Tobin DJ. Int J Cosmet Sci 2008;30(4):233-57; Seiberg M. Int J Cosmet Sci 2013;35(6):532-8

Important markers in HF MC/MelSC

- Dopachromome tautomerase (DCT, TRP-2)
  - Early marker of MC lineage
- KIT
  - Another early marker of MC lineage
  - MelSC survival is KIT-independent

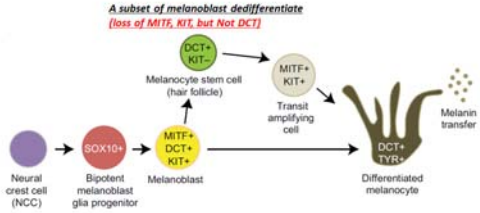


ACK2 (KIT blocking Ab)

Bulge area retains Dct-LacZ+ cell in ACK2 treated mouse

Botchkareva N. FASEB J 2001;15:645-658; Nishmura E. Nature 2002;416:856-860

MC developments in mammals



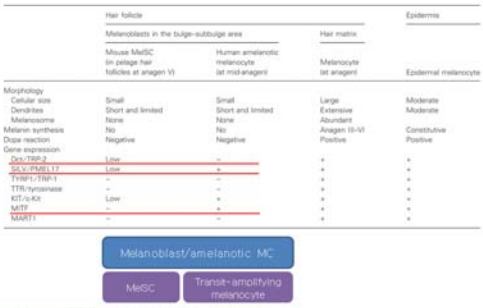
Mort R. Development 2015;142:620-632

'Human' MelSC marker

- Premelanosome protein (PMEL)
  - Encoding gene: *PMEL*
    - = silver locus protein homolog (SILV)
    - = PMEL17
    - = gp100
  - Structural protein of (pre)melanosome
  - PMEL expression is regulated by *MITF*
  - NKI/beteb antibody
- Human MelSC
  - No definite marker
  - Small MITF$^+$ cell
  - Express SILV/gp100/PMEL17
  - Negative for MART1, TRP1, DCT, Dopa reaction

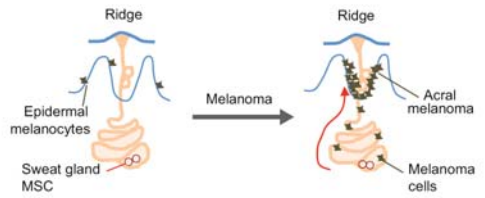
Nishmura E. Science 2005;307:720-724; Pigment Cell Melanoma Res. 2011;24:401-410

Murine MelSCs vs human amelanotic MC



Nishmura E. Pigment Cell Melanoma Res. 2011;24:401-410

Additional source of MelSC

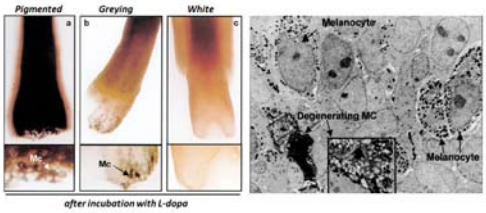


Okamoto N. Pigment Cell Melanoma Res. 2014;27:1039-50

Hair greying

- Vurnerable characteristics of HF MCs
  - Higher 'work burden': as few as 100 MCs provide melanin to a long pigmented hair shaft
  - Exposure to toxic metabolite: more pooled melanosomes within HF MCs
  - ~10 hair cycles before the initiation of greying
- Grey hairs: diluted pigment content (under-pigmented)
- White hairs: total lack of pigment deposition

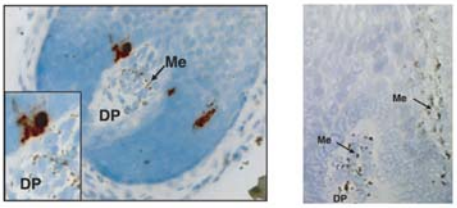
Morphology of canities (1)



- *Reduction in the number and tyrosinase activity of hair bulb MCs*
- *Increased of degenerating melanocytes*

Tobin DJ. Exp Gerontol 2001;36:29-54

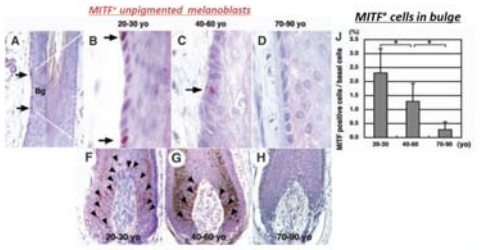
Morphology of canities (2)



- *MCs with hypertrophic with blunted dendrites (gp100 stain) before permenent disapearing*
- *Lack of MC, but melanin incontinence in DP*

Tobin DJ. Int J Cosmet Sci 2008;30(4):233-57

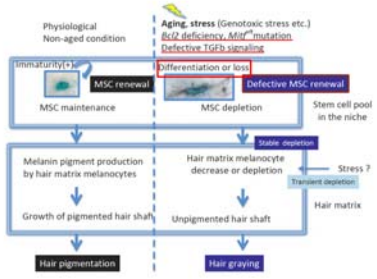
Incomplete MelSC Maintenance in Niche



•MITF+ cells per basal keratinocytes in bulge is decreased (not in infundibulum) in aged HF

Nishimura E. Science 2005;307:720-724

Defective MelSC renewal



Nishimura E. Science 2005;307:720-724; Pigment Cell Melanoma Res. 2011;24:401-410

Loss of BCL-2 in greying

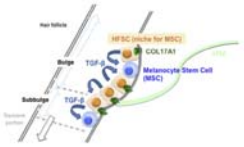
- *Appearance of the Bcl-2-deficient mouse- greying hair*

- *Bcl2-/- follicles in the second hair cycle lack undifferentiated Dct-lacZ+ melanoblasts in the stem-cell niche*
- *Bcl2 might be important for survival of MelSCs*

Nakayama K. Proc Natl Acad Sci U S A. 1994;91:3700-4; Nishimura E. Science 2005;307:720-4

Colocalization of MelSC & HFKSC

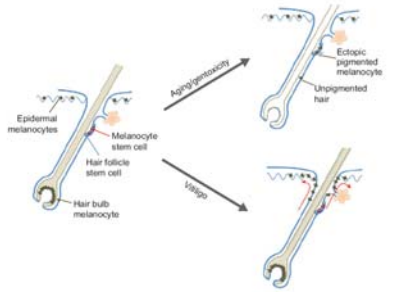
- HFKSC provide a functional niche with MelSC



- *HFKSCs provide COL17A1-dependent niche for MSCs though TGF-b signaling*
- *TGF-b from HFKSCs is critical for the maintenace of MelSC quiescence and immaturity*

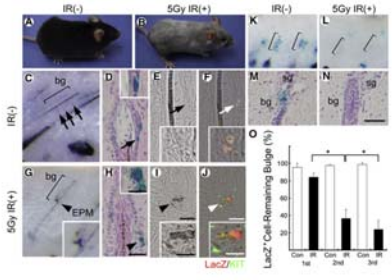
Tanimura S, Nishimura E. Cell Stem Cell 2011;8:177-187

Ectopic pigmented MC in bulge



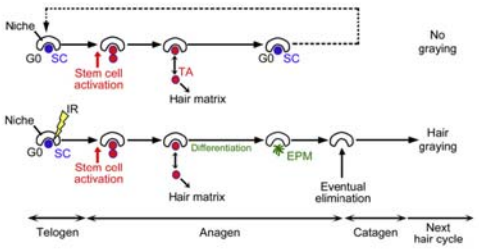
Mort R. Development 2015;142:620-632

Genotoxic stress induces ectopic pigmentation of MSCs in Niche



Inomata K. Cell 2009;137(6):1088-99.

SC differentiation under genotoxic stress



Inomata K. Cell 2009;137(6):1088-99.

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