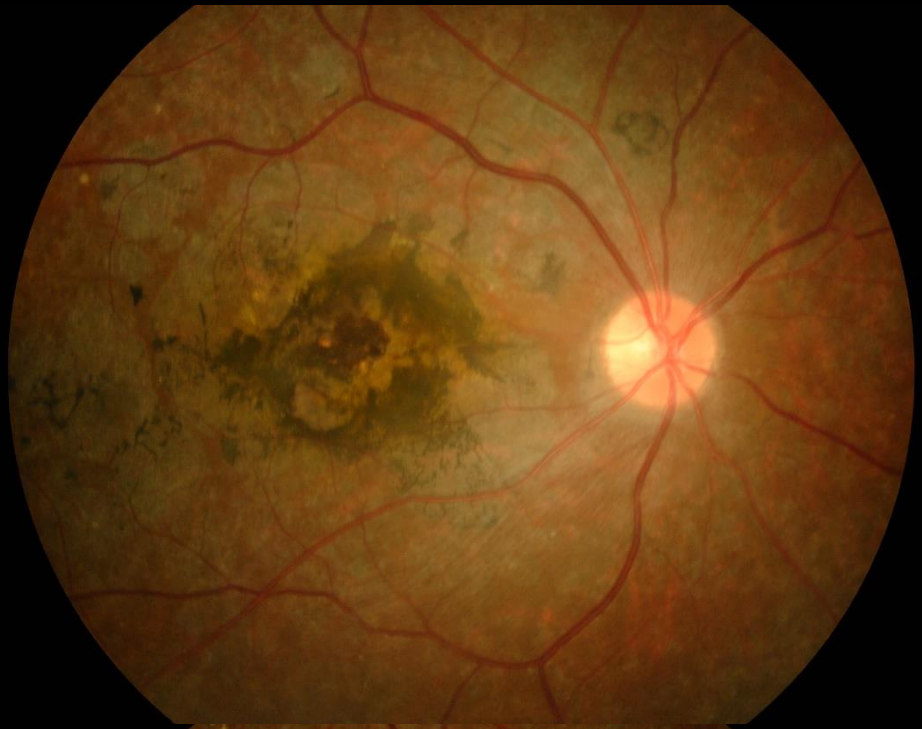
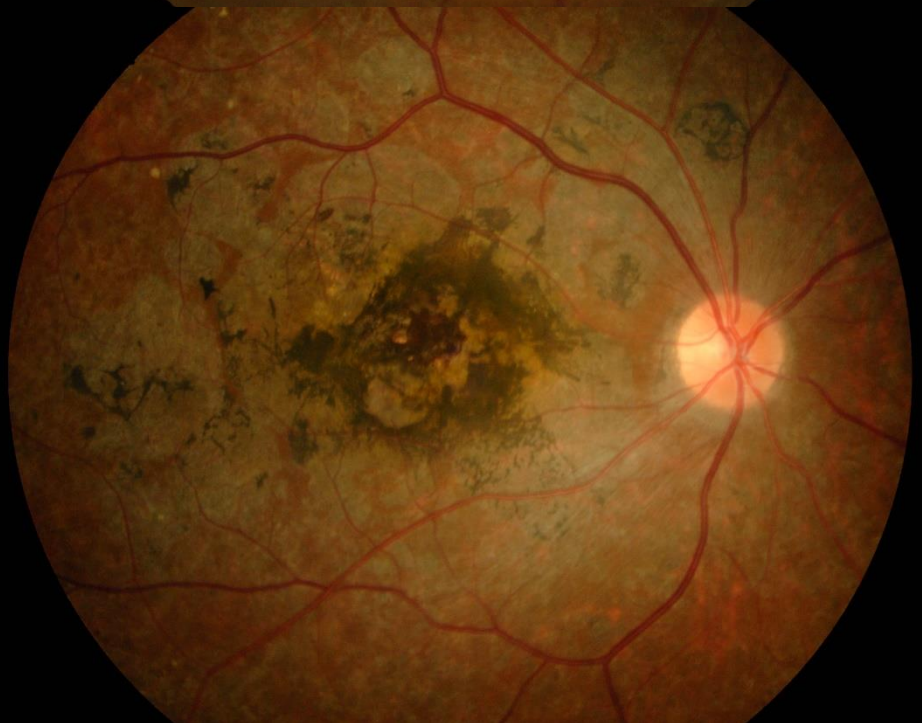




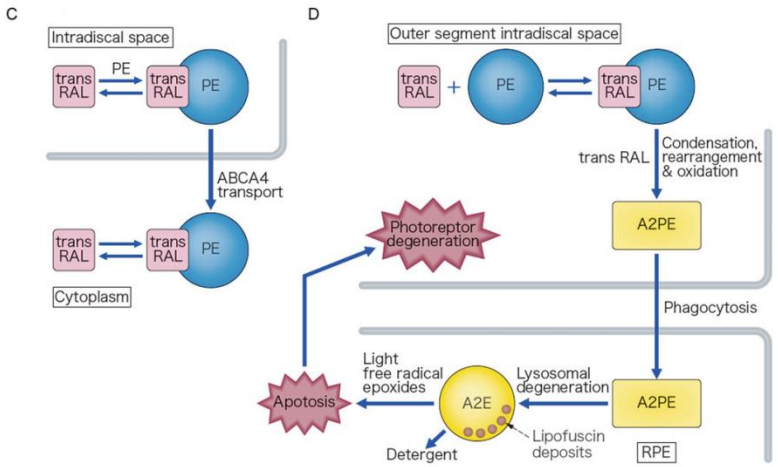
Long-term safety and tolerability of subretinal transplantation of embryonic stem cell-derived retinal pigment epithelium (hES-RPE) in Asian Stargardt disease patients

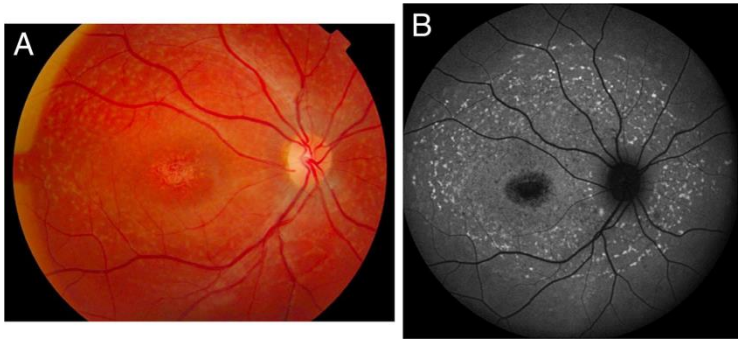
Youngje Sung MD MS
Won Kyung Song MD PhD
Retinal Clinical Trial Lab (RCTL)
CHA Bundang Medical Center
CHA University
Seongnam, Republic of Korea

Stargardt Disease (STGD1; MIM 248200)

- **m/c** inherited form of juvenile macular dystrophy
- A prevalence of **1 in 8000–10000**
- Associated with disease-causing mutations in the **ABCA4** gene
- **Autosomal recessive** mode of inheritance
- Both clinically and genetically highly **heterogeneous**
- **Bilateral central visual loss**, dyschromatopsia, central scotoma
- **No established treatment**
- Characteristic macular atrophy and yellow–white flecks at the level of the retinal pigment epithelium (**RPE**) at the posterior pole

	Childhood	Early adulthood	Late adulthood
Prevalence	Common	⟷	Least
Prognosis	Poor	⟷	Better





British Journal of Ophthalmology 101.1 (2017): 25-30.
Advances in Vision Research, Volume II. Essentials in Ophthalmology. Springer, Singapore.

Clinical Trials in CHA Bundang Medical Center

RPE Clinical Trials

hES-RPE

(Human Embryonic Stem Cell Derived Retinal Pigment Epithelium)

Age-related macular degeneration

(Advanced dry AMD)

2012~

Inherited macular degeneration

(Stargardt Disease, SMD)

2013~

SCNT-RPE

(Somatic Cell Nuclear Transfer Stem Cell Derived Retinal Pigment Epithelium)

Age-related macular degeneration

(Advanced dry AMD)

2017~

Publications from the clinical trials in Bundang CHAMC

STEM CELL REPORTS

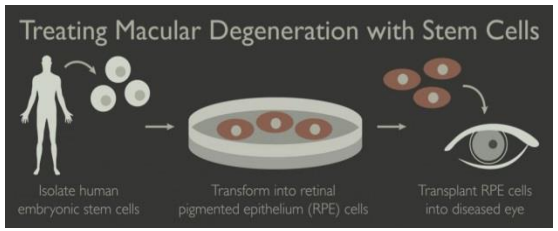
Cell PRESS

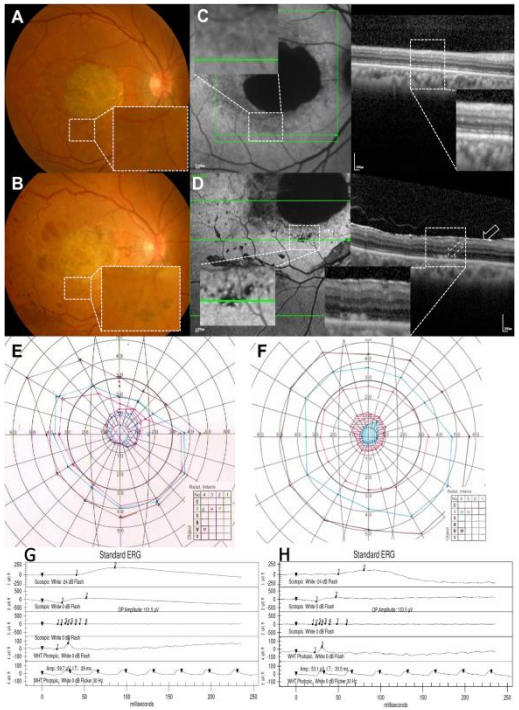
Open Access

Volume 4, Issue 5, 12 May 2015, Pages 860–872

Article

Treatment of Macular Degeneration Using Embryonic Stem Cell -Derived Retinal Pigment Epithelium: Preliminary Results in Asian Patients





Participants : total of 4
- 2 Dry AMD
- 2 SMD

IP :
- hES-RPE suspension $5x10^4$ cells

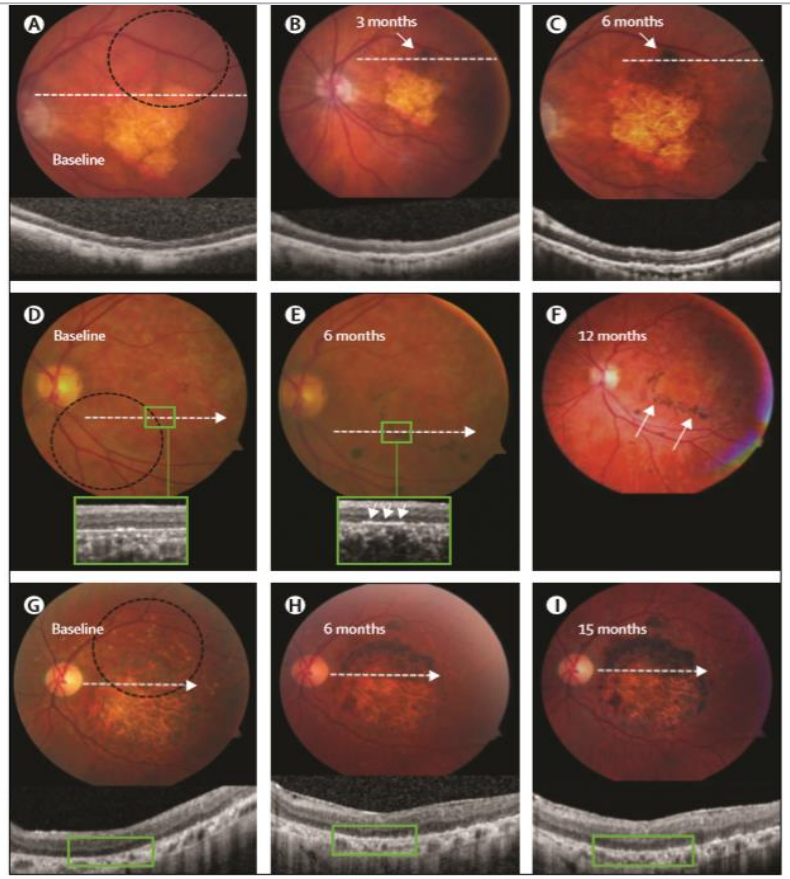
Follow up :
- 12 months

Outcome:
- BCVA (ETDRS)
  Dry AMD +1 (FE -5), +9 (FE -20)
  SMD +12 (FE +9), +19 (FE =+9)
- 3/4 eyes subretinal pigmentation

Adverse events
- 1 eye choroidal neovascularization (CNV) requiring anti-VEGF
- 2 eyes epiretinal membrane (ERM) with pigmentations

Stem cell reports 4.5 (2015): 860-872.

The first Publications from hES-RPE Trials (U.S.)



Participants : total of **18**
- 9 Dry AMD (77 Y; 70-88)
- **9 SMD (50 Y; 20-71)**

IP : hES-RPE suspension
-3 eyes each with $5x10^4$, $10x10^4$, $15x10^4$ cells

Follow up : 22 months
- 4 < 12m.; 12 12-36 m.; 2 >36m.

Outcome BCVA at 12 months :
< Dry AMD >
3 eyes improved > 15 letters
1 eye improved 13 letters
3 eyes stable
< SMD >
3 eyes improved ≥ 15 letters
3 eyes stable
1 eye decreased by more than 10 letters

Adverse Events
- No cell related adverse proliferation, rejection, or serious ocular or systemic safety issues
- Adverse events were associated with vitreoretinal surgery and immunosuppression
  : Endophthalmitis 1, preretinal pigmentation 3, cataract 4, vitreal band 1

❖ 13 (72%)/ 18 patients ; patches of subretinal pigmentation.

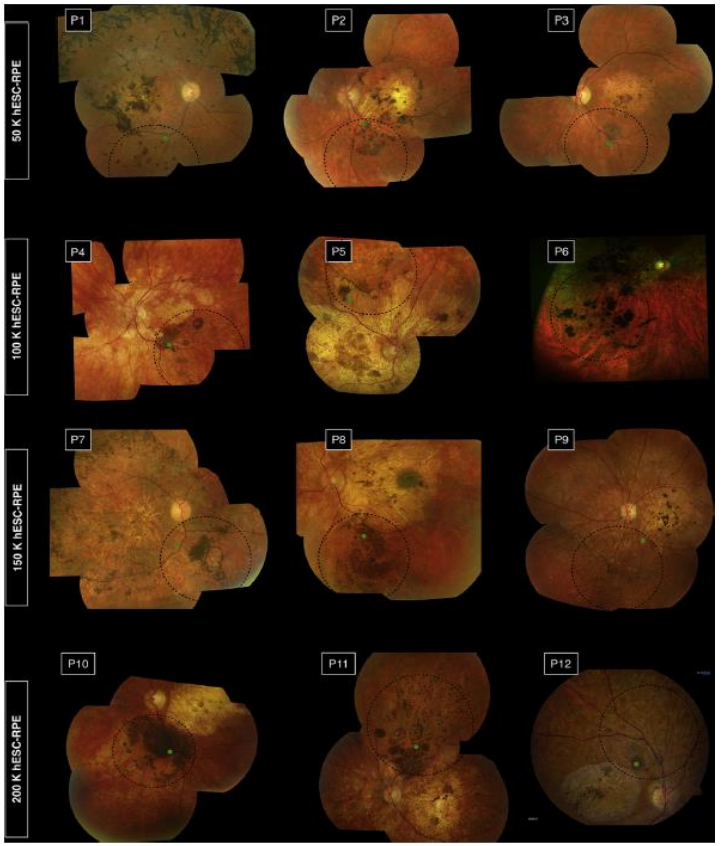
The Lancet 379.9817 (2012): 713-720.
Stem cells 27.9 (2009): 2126-2135.

Following reports from hES-RPE trial (U.K.)

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Transplantation of Human Embryonic Stem Cell-Derived Retinal Pigment Epithelial Cells in Macular Degeneration

Manjit S. Mehat, PhD, FRCOphth,[1,2,3] Venki Sundaram, MD, FRCOphth,[1,2,3] Caterina Ripamonti, PhD,[4] Anthony G. Robson, PhD,[1,2] Alexander J. Smith, PhD,[1,3] Shyamanga Borooah, PhD, FRCOphth,[5] Martha Robinson, PhD,[3] Adam N. Rosenthal, PhD, FRCOG,[6] William Innes, MRCP,[7] Richard G. Weleber, MD,[8] Richard W.J. Lee, PhD, FRCOphth,[1,2,3] Michael Crossland, PhD,[1,2,3] Gary S. Rubin, PhD,[1,2,3] Baljean Dhillon, FRCS,[5] David H.W. Steel, FRCOphth,[7,9] Eddy Anglade, MD,[10] Robert P. Lanza, PhD,[10] Robin R. Ali, PhD,[1,3,11] Michel Michaelides, MD, FRCOphth,[1,2,3] James W.B. Bainbridge, PhD, FRCOphth[1,2,3]



Participants :
- 12 STGD1 (34-53 years)

IP : hES-RPE suspension
3 eyes in each dose of $5x10^4$, $10x10^4$, $15x10^4$, $20x10^4$ cells
+ Systemic immunosuppression for 13 weeks

Follow up: 12 months

Outcome
BCVA : borderline improvement in 4 eyes, unsustained or similar improvement in fellow eyes
Microperimetry ; borderline improve in 1 eye at 3 mo only, others not significant
Static perimetry ; deterioration in 2 patients both eyes, not significant
NEI VFQ-25 ; no significant change
Color vision (n=4) ; no significant change
Subretinal pigmentation in all eyes area α dose (R^2=0.981)

Ophthalmology Volume 125, Number 11, November 2018

Identification of Transplanted hES-RPE in Human

: Following reports from the clinical trials in Bundang CHAMC

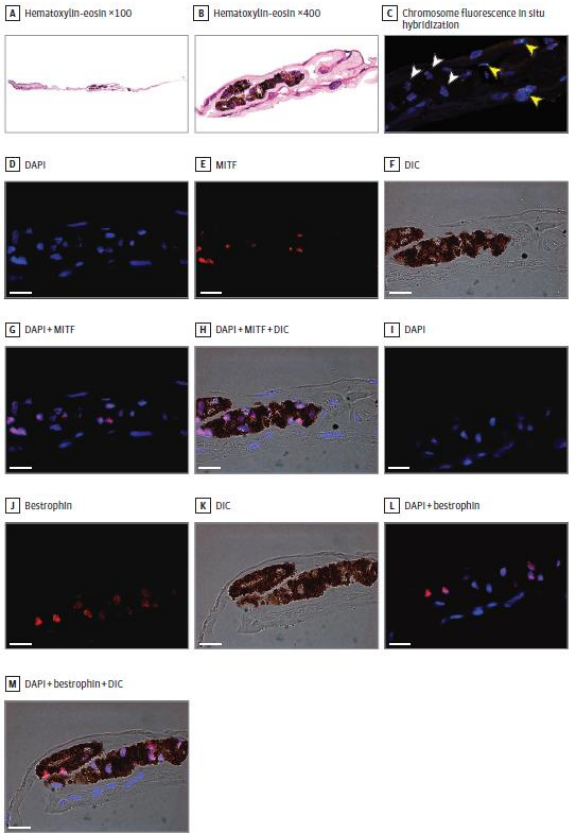
The JAMA Network

JAMA Ophthalmology | Journals | Enter Search Term

March 2017

Survival of Transplanted Human Embryonic Stem Cell–Derived Retinal Pigment Epithelial Cells in a Human Recipient for 22 Months

Sung Han Shim, PhD[1]; Gwangil Kim, MD, PhD[2]; Dong Ryul Lee, PhD[3]; et al



JAMA Ophthalmology 135.3 (2017): 287-289.

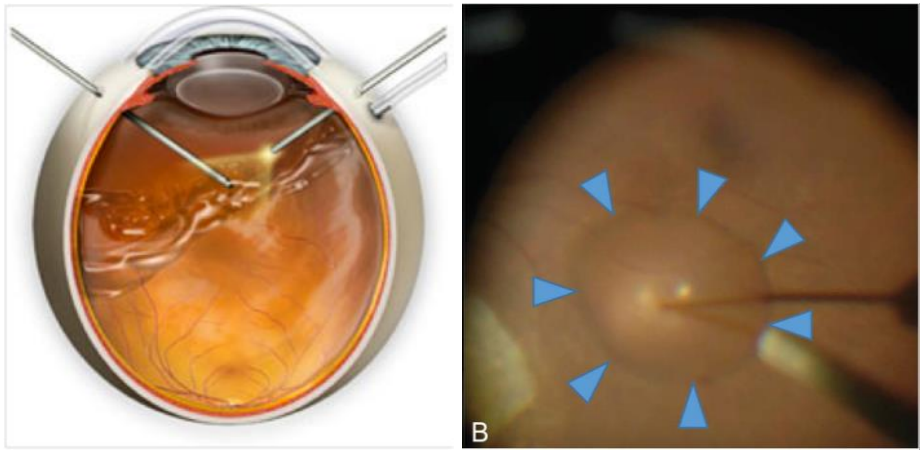
Long-term safety and tolerability of subretinal transplantation of hES-RPE in Asian SMD patients

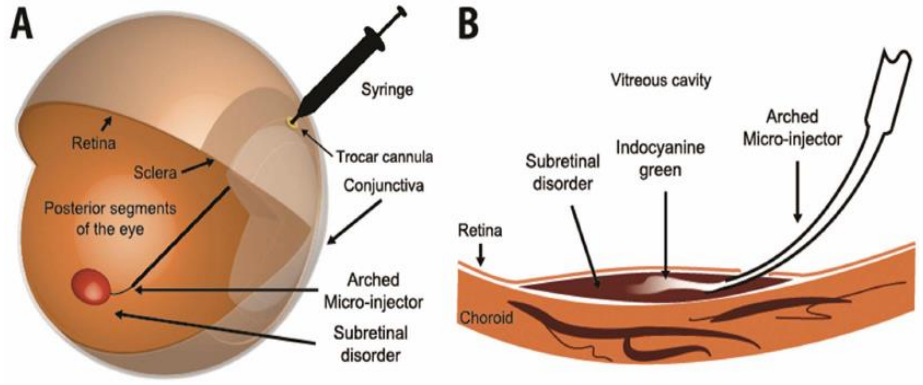
: Following reports from the clinical trials in Bundang CHAMC

Long-term safety and tolerability of subretinal transplantation of embryonic stem cell-derived retinal pigment epithelium in Asian Stargardt disease patients

Youngje Sung [1], Min Ji Lee,[2] Jinjung Choi,[3] Sang Yoon Jung,[3] So Young Chong,[4] Jung Hoon Sung,[5] Sung Han Shim,[6] Won Kyung Song[1]

Br J Ophthalmol 2020;**0**:1–9. doi:10.1136/bjophthalmol-2020-316225





Participants:
- total of 3 (age range: 40-45)

IP:
- hES-RPE suspension $5x10^4$ cells

Route:
- subretinal transplantation after vitrectomy

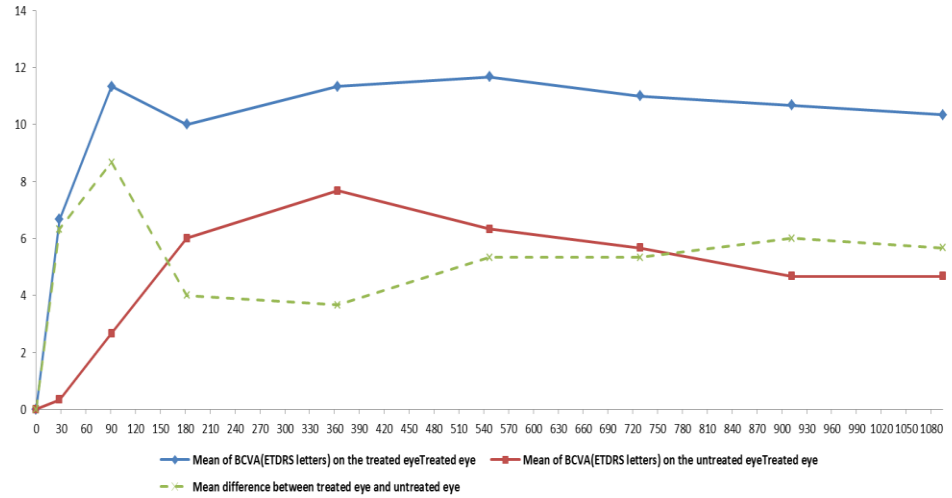
Follow up:
- 36 months

Outcome:
- Primary : safety & tolerability:
  Physical, laboratory examinations

- Ophthalmic examinations:
  NEI VFQ-25, visual acuity, visual field, fundus photography, fluorescein angiography, optical coherence tomography, autofluorescence

PloS one 9.8 (2014): e104145.
Retina 39 (2019): S174-S176.
https://retinaspecialists.com.au/vitrectomy-surgery/

Long-term safety and tolerability of subretinal transplantation of hES-RPE in Asian SMD patients

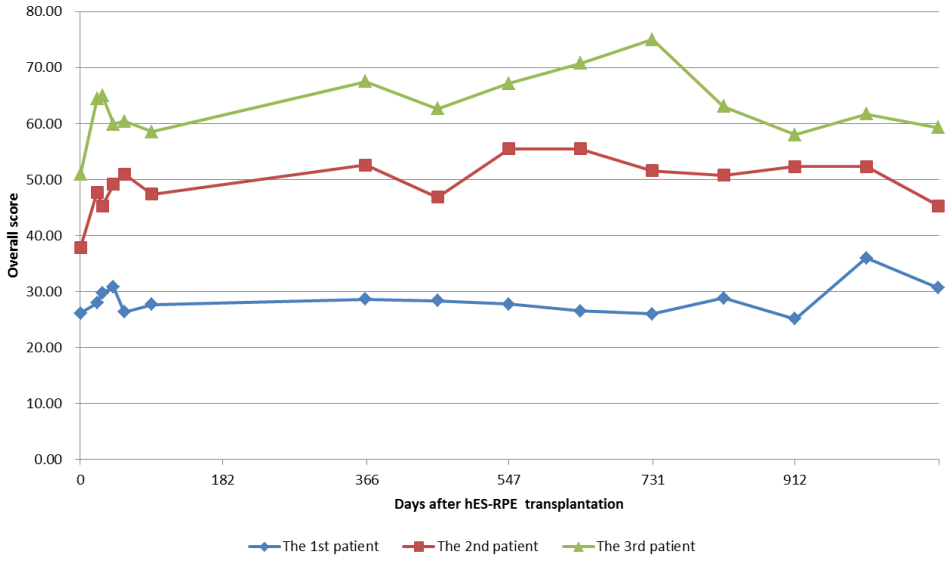


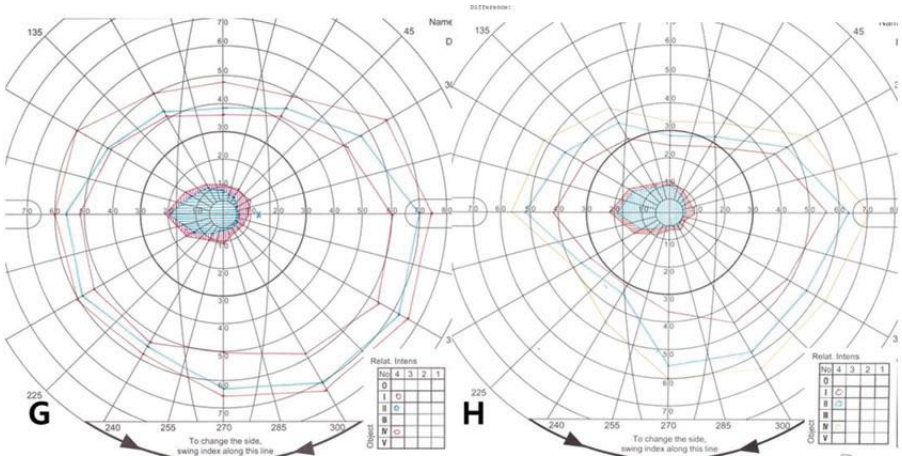
Outcome:

- No severe systemic AEs
- No severe AEs related to immunosuppression
- No severe ophthalmic AEs related to hES-RPE
- No abnormal proliferation and rejection

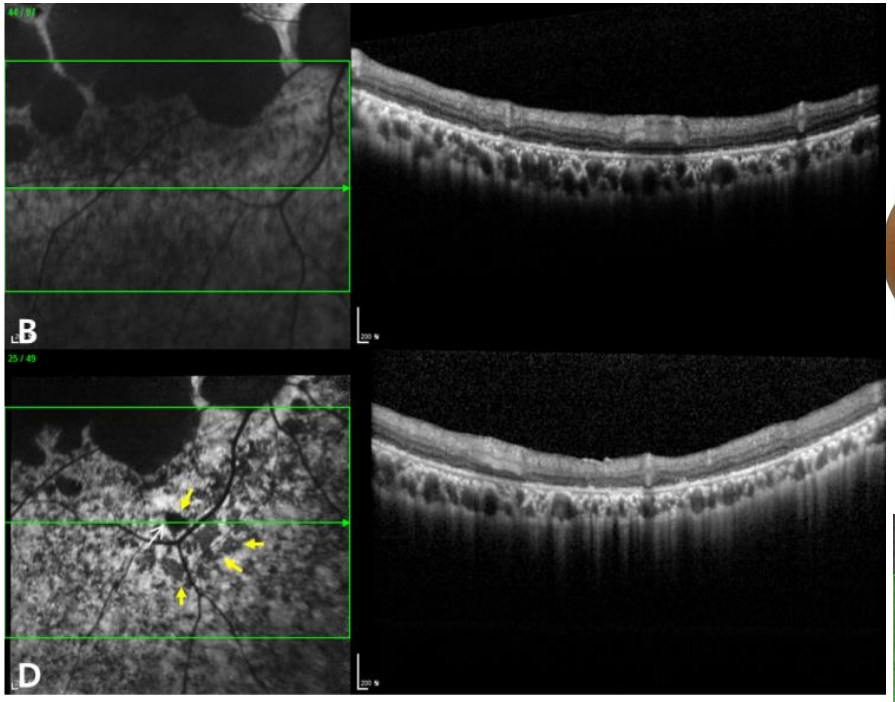
Functional:

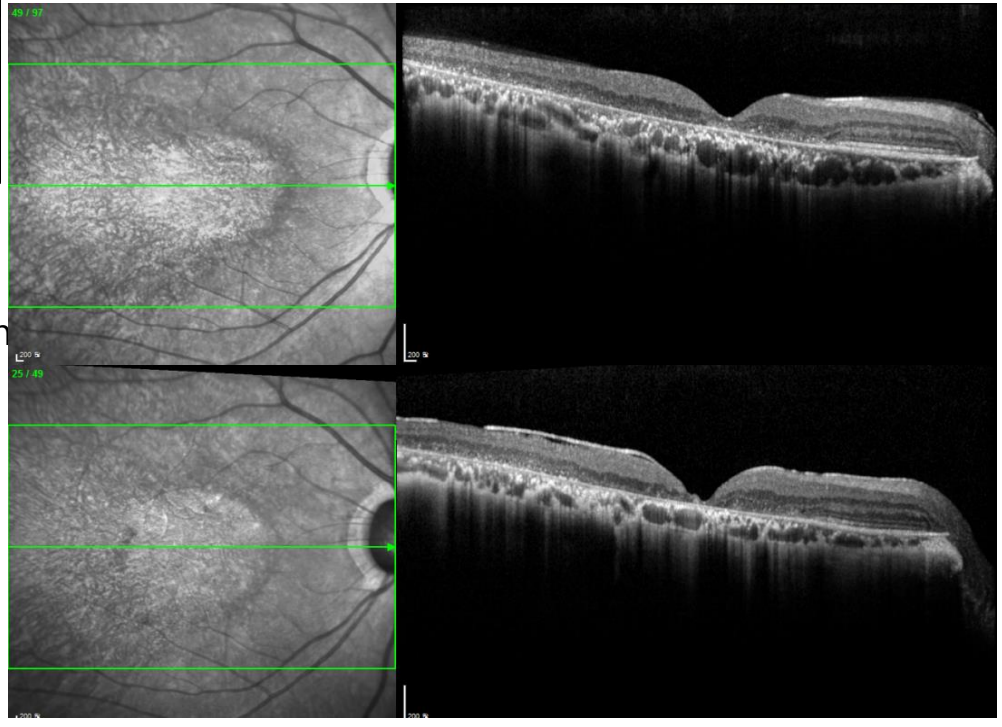
- BCVA : +9 (FE +7), +17 (FE +2), +5 (FE +5)
- NEI VFQ-25 : consistent with BCVA in Pt.2.
- Visual Field
- Electroretinogram





Long-term safety and tolerability of subretinal transplantation of hES-RPE in Asian SMD patients





Anatomical:

- Subretinal pigmentation (1 eye)
- Epiretinal membrane with preretinal pigmentation (1 eye)

Significant adverse events:

- Rhegmatogenous retinal detachment (1 eye)
- Epiretinal membrane with pigmentation (1 eye)

Genetic Research of Korean Patients with Stargardt Disease

Ophthalmologica

Research Article

Ophthalmologica
DOI: 10.1159/000490073

Received: February 14, 2018
Accepted after revision: May 9, 2018
Published online: July 4, 2018

Clinical and Genetic Characteristics Analysis of Korean Patients with Stargardt Disease Using Targeted Exome Sequencing

Youngje Sung[a] Seung Woo Choi[c] Sung Han Shim[b] Won Kyung Song[a]

한국인 최초 스타가르트 유전-표현형 분석 연구
ABCA4 mutations were confirmed in 17 of 24 patients, and
12 novel mutations were identified

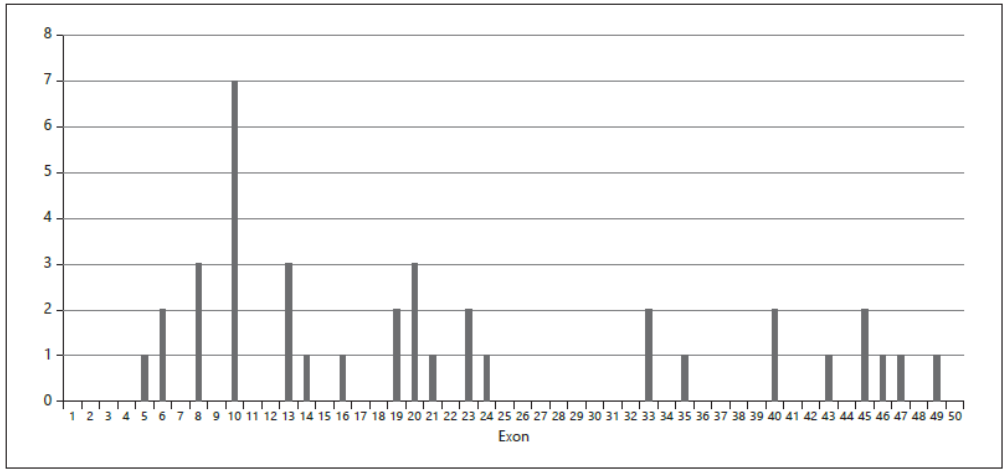


Fig. 4. Distribution and frequency of *ABCA4* gene mutations.

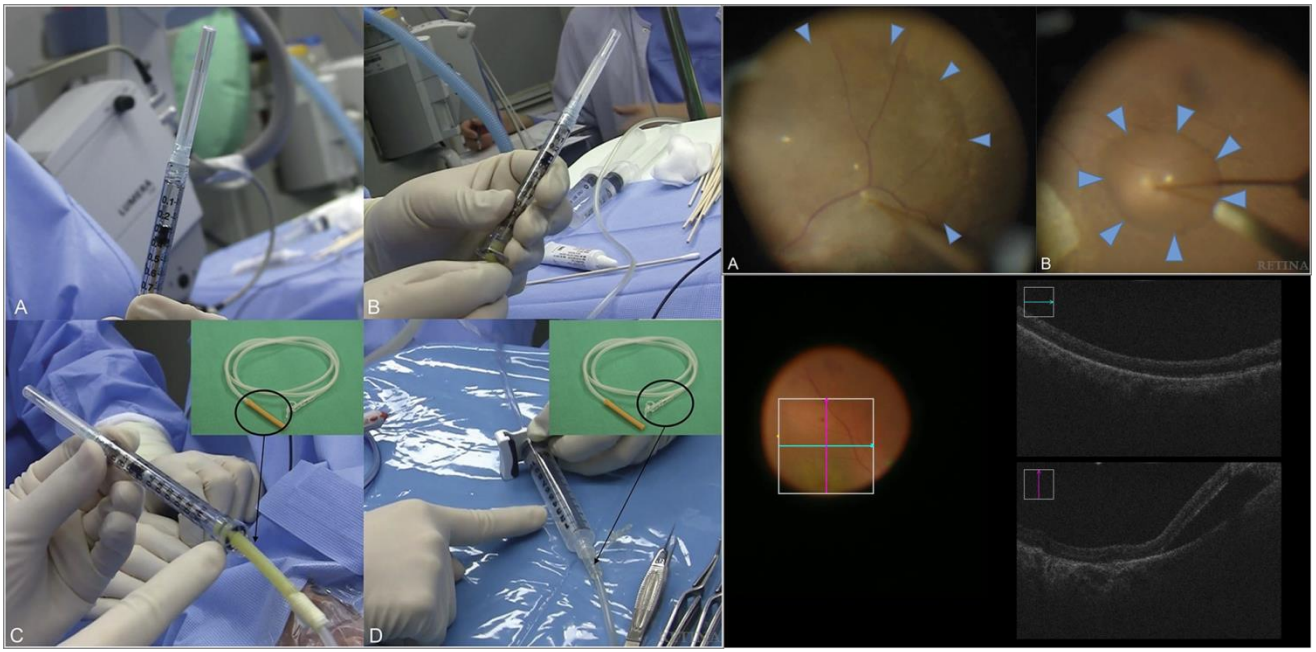
Table 2. List of mutations identified from exome sequencing of the *ABCA4* gene

Patient No.	Gene	Exon	cDNA sequence change	Amino acid change	Domain	Note	Mutation type	PolyPhen2 prediction	MutationTaster prediction
P001	*ABCA4*	8	c.983A>T	p.Glu328Val	extracellular loop	reported	–	–	–
	ABCA4	13	c.1933G>A	p.Asp645Asn	extracellular loop	reported	–	–	–
	ABCA4	21	c.3106G>A	p.Glu1036Lys	ATP-binding domain	reported	–	–	–
P002	*ABCA4*	19	c.2894A>G	p.Asn965Ser	extracellular loop	reported	–	–	–
	ABCA4	35	c.4972A>C	p.Ser1658Arg	–	novel	missense	possibly damaging	DC
P003	*ABCA4*	20	c.3035_3037delACA	p.Asn1012del	ATP-binding domain	novel	deletion	–	DC
	ABCA4	13	c.1804C>T	p.Arg602Trp	extracellular loop	reported	–	–	–
P004	*ABCA4*	19	c.2974A>C	p.Thr972Pro	ATP-binding domain	novel	missense	probably	DC
	ABCA4	43	c.5929G>A	p.Gly1977Ser					
P011	*ABCA4*	10	c.1268A>G	p.His423Arg	extracellular loop	reported	–	–	–
	ABCA4	40	c.5656G>A	p.Gly1886Arg	transmembrane domain	reported	–	–	–
	ABCA4	45	c.6146_6146delA	p.Lys2049Arg	ATP-binding domain	novel	deletion	benign	DC
P012	*ABCA4*	10	c.1268A>G	p.His423Arg	extracellular loop	reported	–	–	–
	ABCA4	10	c.1309C>A	p.Gln437Lys	extracellular loop	novel	missense	benign	DC
P013	*ABCA4*	6	c.635G>A	p.Arg212His	extracellular loop	reported	–	–	–
	ABCA4	12	c.1699G>A	p.Val567Met	extracellular loop	reported	–	–	–
P015	*ABCA4*	6	c.635G>A	p.Arg212His	extracellular loop	reported	–	–	–
	ABCA4	49	c.6764G>T	p.Ser2255Ile	–	reported	–	–	–
P016	*ABCA4*	5	c.560G>A	p.Arg187His	extracellular loop	novel	missense	benign	DC
	ABCA4	6	c.635G>A	p.Arg212His	extracellular loop	reported	–	–	–
	ABCA4	10	c.1268A>G	p.His423Arg	extracellular loop	reported	–	–	–
P017	*ABCA4*	8	c.880C>T	p.Gln294*	extracellular loop	novel	stop-gain	–	DC
	ABCA4	10	c.1294G>A	p.Glu432Lys	extracellular loop	reported	–	–	–
	ABCA4	33	c.4685T>A	p.Ile1562Thr	extracellular loop	reported	–	–	–
P018	*ABCA4*	10	c.1268A>G	p.His423Arg	extracellular loop	reported	–	–	–
	ABCA4	20	c.3035_3037delACA	p.Asn1012Ile	ATP-binding domain	novel	deletion	–	DC
	ABCA4	47	c.6389T>A	p.Met2130Lys	–	novel	missense	probably damaging	DC
P020	*ABCA4*	8	c.880C>T	p.Gln294*	extracellular loop	novel	stop-gain	–	DC
	ABCA4	23	c.3398T>C	p.Ile1133Thr	extracellular loop	novel	missense	benign	DC
P021	*ABCA4*	14	c.1958G>A	p.Arg653His	transmembrane domain	reported	–	–	–
	ABCA4	40	c.5656G>A	p.Gly1886Arg	transmembrane domain	reported	–	–	–
P022	*ABCA4*	13	c.1933G>A	p.Asp645Asn	extracellular loop	reported	–	–	–
	ABCA4	44	c.6146-6146delA	p.Lys2049Arg	ATP-binding domain	novel	deletion	benign	DC
P023	*ABCA4*	20	c.3035_3037delACA	p.Asn1012Ile	ATP-binding domain	novel	deletion	–	DC
	ABCA4	24	c.3547G>T	p.Gly1183Cys	–	reported	–	–	–
	ABCA4	46	c.6289C>T	p.Pro2097Ser	ATP-binding domain	novel	missense	probably damaging	DC
P024	*ABCA4*	10	c.1268A>G	p.His423Arg	extracellular loop	reported	–	–	–
	ABCA4	33	c.4748T>C	p.Leu1583Pro	extracellular loop	reported	–	–	–
P026	*ABCA4*	16	c.2384G>A	p.Ser795Asn	transmembrane domain	novel	missense	possibly damaging	DC
	ABCA4	23(?)	c.3470T>G	p.Leu1157*	–	novel	stop-gain	–	DC

DC, disease causing.

Ophthalmologica 241.1 (2019): 38-48.

Patents



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(11) 공개번호 10-2018-0026017
(43) 공개일자 2018년03월12일

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A61K 35/28 (2015.01) *A61K 48/00* (2006.01)
A61M 5/145 (2006.01) *A61M 5/168* (2006.01)
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전체 청구항 수 : 총 19 항

(54) 발명의 명칭 **약액 주입 장치 및 방법**

(57) 요 약

본 발명의 일 실시예는, 양단이 개방되는 주사기 몸통부와, 주사기 몸통부의 내면에 접한 상태에서 주사기 몸통부의 길이 방향을 따라 슬라이딩 가능한 슬라이딩부와, 주사기 몸통부의 일단에 연결되어 주사기 몸통부 내부의 약액 공간과 연통되고, 타단은 체내로 삽입되는 삽입부와, 주사기 몸통부의 타단에 연결되고, 주사기 몸통부 내부의 점성유체 공간과 연통되어 점성유체 공간에 점성유체를 주입하는 주입부를 포함하고, 슬라이딩부는 약액 공간과 점성유체 공간을 구분하며, 약액 공간에는 세포치료제 및 유전자치료제 중 적어도 하나를 포함하는 약액이 주입되는 약액 주입 장치를 개시한다.

대 표 도 - 도1

Semiautomated Subretinal Fluid Injection Method Using Viscous Fluid Injection Mode

HEE J. KWON, MD, OH W. KWON, MD, PHD, WON K. SONG, MD, PHD

Retina. *2019 Oct;39 Suppl 1:S174-S176.*

Patents

(19) 대한민국특허청(KR)
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(65) 공개번호 10-2018-0112154
(43) 공개일자 2018년10월12일
(56) 선행기술조사문헌
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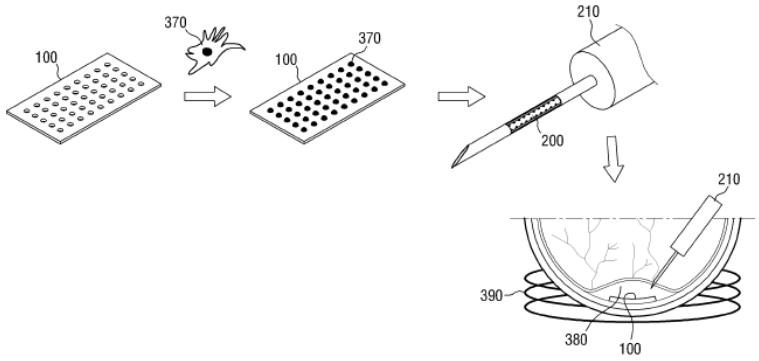
(54) 발명의 명칭 **형상변형이 가능한 스캐폴드**

(57) 요 약

본 발명은 스캐폴드에 관한 것으로, 보다 상세하게는 형상변형이 가능한 스캐폴드, 그 제조방법 및 변형복원 방법에 관한 것이다. 이를 위해, 제1 형태를 갖는 스캐폴드(100); 스캐폴드(100)에 담지되어 제1형태와 다른 제2 형태로 스캐폴드(100)를 변형시키는 변형수단; 스캐폴드(100)에 담지되어 외부의 자력에 반응하는 자성체(20); 및 스캐폴드(100)에 담지되는 세포 또는 약물;을 포함하는 것을 특징으로 하는 형상변형이 가능한 스캐폴드가 제공된다.

대 표 도 - 도9b



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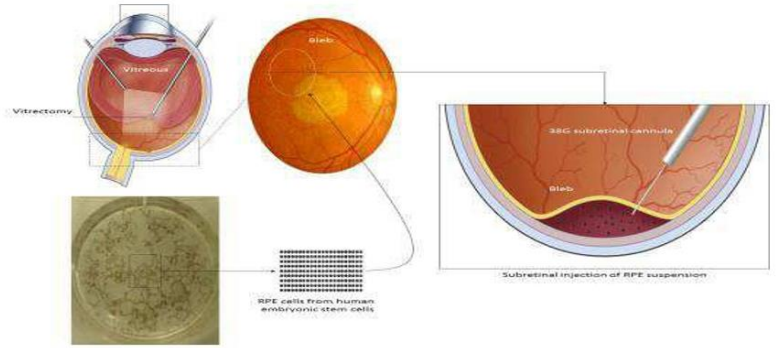

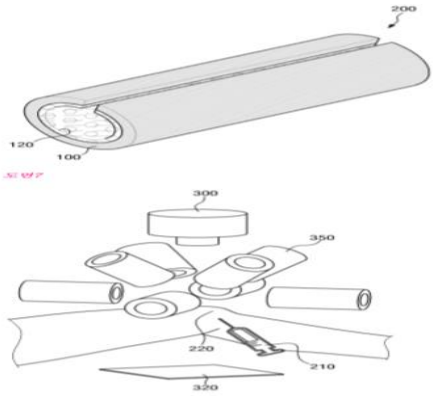

망막 하 약물(세포)주입 전달성을 높이기 위한 형상변형 가능한 스캐폴드

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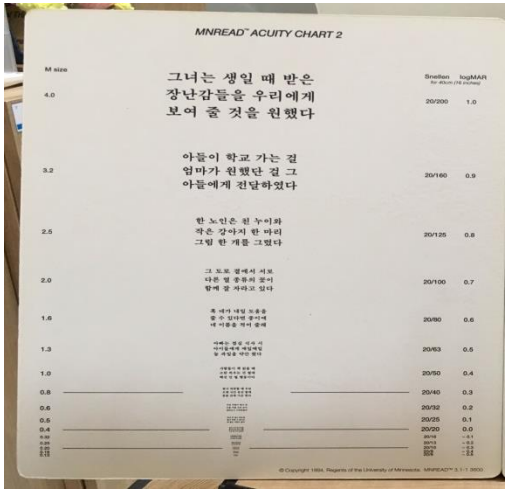

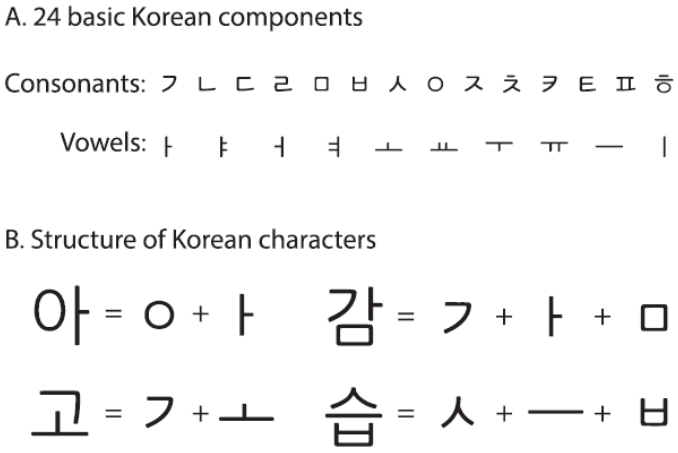

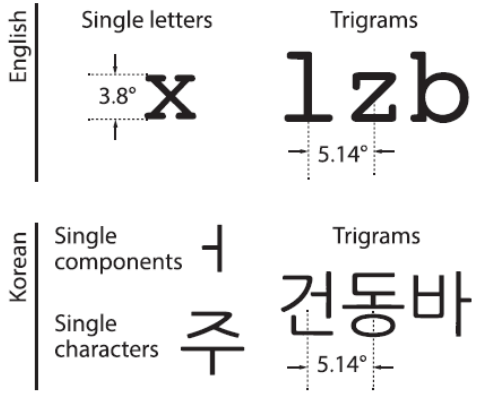

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