치매의 최신 지견

박 영 호
서울의대

Dementia

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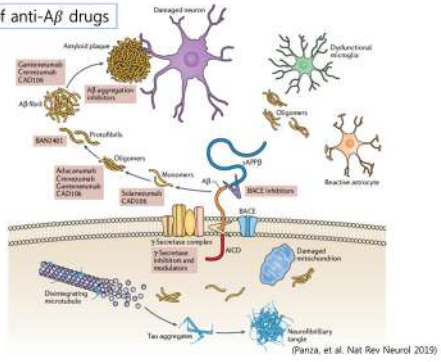
내용

- Treatment
- Genetics
- Pathophysiology

Treatment

치매 신약이 개발되었나요?

Mechanism of action of anti-Aβ drugs



(Panza, et al. Nat Rev Neurol 2019)

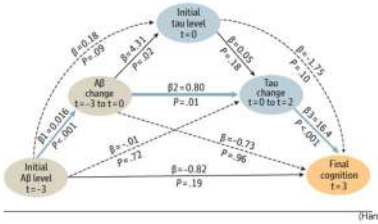
Aducanumab은 왜 실패했을까?

- Aβ의 축적이 인지 저하를 일으킨다는 기존 가설(amyloid hypothesis)이 잘못되었다.
- 이미 증상이 시작된 환자에서 투여하는 것은 너무 늦었다.
- 다른 기전의 치료제(tau, inflammation)와 병용 요법 (combination therapy)이 필요하다.

(Selkoe Nat Rev Neurol 2019)

Aβ, tau and cognitive decline in a longitudinal study

Figure 3. Overview of Sequential Associations Between Amyloid-β (Aβ), Tau, and Cognition



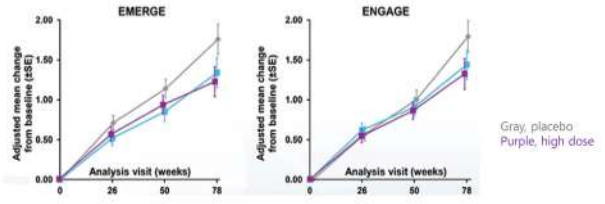
(Hanseeuw, et al. JAMA Neurol 2019)

A resurrection of aducanumab for Alzheimer's disease

- 중간분석에 쓴 자료는 2018년 12월 26일까지 임상연구 완료된 945명(ENGAGE), 803명(EMERGE) 분석
- 이후 2019년 3월 21일 연구 중단까지 139명(ENGAGE), 179명(EMERGE)이 임상연구 완료
- 위약군에 비해 치료군에서 CDR-SB(primary outcome) 23% 개선 (EMERGE only)

(Schneider Lancet Neurol 2019)

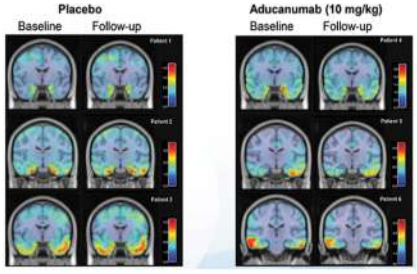
Aducanumab의 재도전



Gray, placebo
Purple, high dose

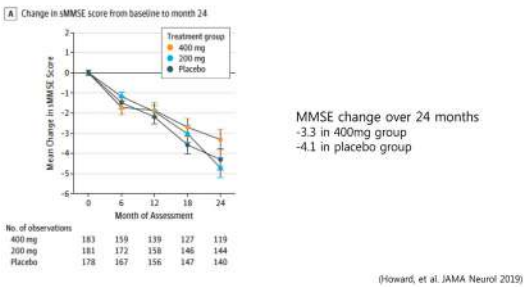
(Howard, et al. Nat Rev Neurol 2019)
(https://www.alzforum.org/)

14개월 동안 고용량의 aducanumab 투여 후 내측두부의 tau 감소



(https://www.alzforum.org/)

Minocycline (mainly for anti-inflammation)



MMSE change over 24 months
-3.3 in 400mg group
-4.1 in placebo group

(Howard, et al. JAMA Neurol 2019)

Technologies in dementia care

Table 1 | Technologies that can support people with dementia and carers

Device name (manufacturer)	Functions	Developed for	Level of evidence[a]	Refs
Monitoring				
Google Home (Google)	Calendar reminders, weather and controls lighting and heating through smart phone	General use	Level VII	NR
Find My Turnal Watch (Turnal)	GPS monitoring. Can aid orientation, location tracking and fall detection; offers 24/7 support	Cognitively impaired	Level V	
Wireless movement sensors (Just Checking)	Text and e-mail messages to alert carer. Information on activity and when different rooms are used	Cognitively impaired	Level II	
Assistive robotics				
Care-O-Bot (Fraunhofer Institute for Manufacturing Engineering and Automation)	A range of applications, including fetch and carry, monitoring, reminders and communication	Older people and cognitively impaired	Level V	
RAMCIP (EU Horizon 2020 project)	Reminds individuals about daily tasks such as taking medications, brings food and food, can detect falls and offers communication via video conference	MCI	Level VI	
Hoist and Rollout (RIKEN-SRK)	Can transfer frail people from floor to chair or bed	Older people and disabled	Level VII	NR
Assistive innovations				
Obi	Robotic spoon that allows automatic or semi-automatic feeding	Disabled	Level VII	NR
MARIO (National University of Ireland)	Entertainment and reminders	Older people and cognitively impaired	Level VI	
Hobbs (Consequential Robotics)	Autonomous robotic dog that reminds user about medications, hydration and temperature, and can contact emergency services	Cognitively impaired	Level VII	NR

(Moyle Nat Rev Neurol 2019)

RAMCIP (Robotic Assistant for mild cognitive impairment Patients at home)

<Tracking of large object state>

<Detection of small object and tracking its components>

(https://link.springer.com/conference/eccv)

<Human tracking used for action recognition>

<RAMCIP의 활동>
1, 응급 상황 발견; 2, 전원 끄기; 3, 전등 끄기; 4, 물건 제자리에 두기; 5, 약 가져오기
6, 요리 중 이상 발견; 7, 떨어진 물건 줍기; 8, 물 가져오기; 9, 간식 가져오기; 10, 인지훈련 제공

(https://link.springer.com/conference/eccv)

Genetics

치매는 유전되나요?

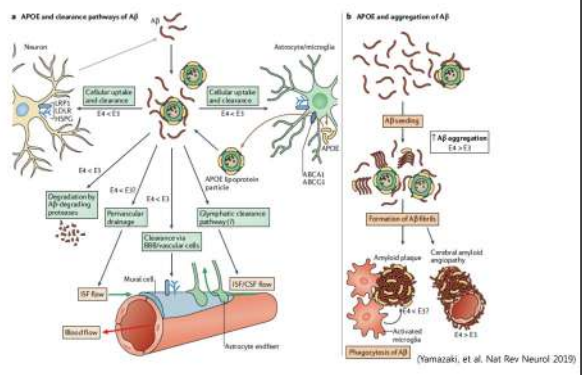
APOE – Greater impact in neuropathologically confirmed group

Table 1 Association of APOE genotypes and allelic doses compared to the APOE3/3 genotype.

APOE	Neuropathologically confirmed group			Neuropathologically unconfirmed group		
	OR	95% CI	P	OR	95% CI	P
Genotype						
2/2	0.13	0.05–0.36	6.3×10^{-5}	0.52	0.30–0.90	0.02
2/3	0.39	0.30–0.50	1.6×10^{-12}	0.63	0.53–0.75	2.2×10^{-7}
2/4	2.68	1.65–4.36	7.5×10^{-5}	2.47	2.02–3.01	5.7×10^{-19}
3/4	6.13	5.08–7.41	2.2×10^{-75}	3.55	3.17–3.98	2.3×10^{-105}
4/4	31.22	16.59–58.75	4.9×10^{-26}	10.70	9.12–12.56	7.5×10^{-186}
Allelic dose						
2	0.38	0.30–0.48	1.1×10^{-15}	0.64	0.58–0.72	2.2×10^{-16}
4	6.00	5.06–7.12	3.4×10^{-90}	3.43	3.26–3.60	$<10^{-300}$

For genotypic association tests, odds ratio (OR), 95% confidence interval (CI), and *P* value (P) for each APOE genotype compared to the APOE3/3 genotype were calculated under a logistic regression model.
For allelic association tests, OR, CI, and *P* associated with APOE2 allelic dose in APOE4 non-carriers (APOE2/2 < 2/3 < 3/3) and APOE4 allelic dose in APOE2 non-carriers (APOE4/4 > 3/4 > 3/3) in an additive genetic model were generated under a logistic regression model.

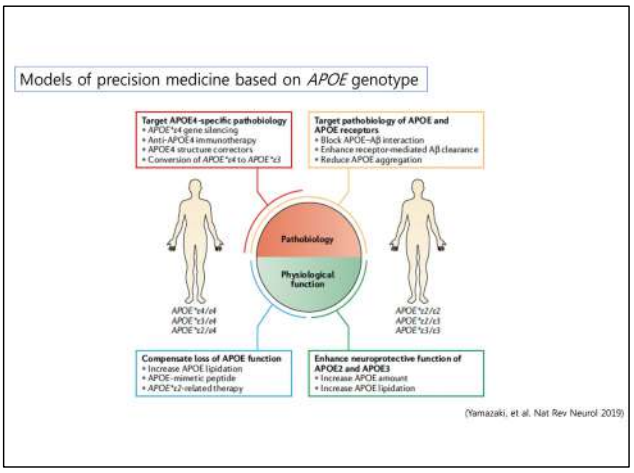
(Reiman, et al. Nat Comm 2020)



(Yamazaki, et al. Nat Rev Neurol 2019)

Effects of APOE4 on AD pathogenesis pathways

(Yamazaki, et al. Nat Rev Neurol 2019)



(Yamazaki, et al. Nat Rev Neurol 2019)

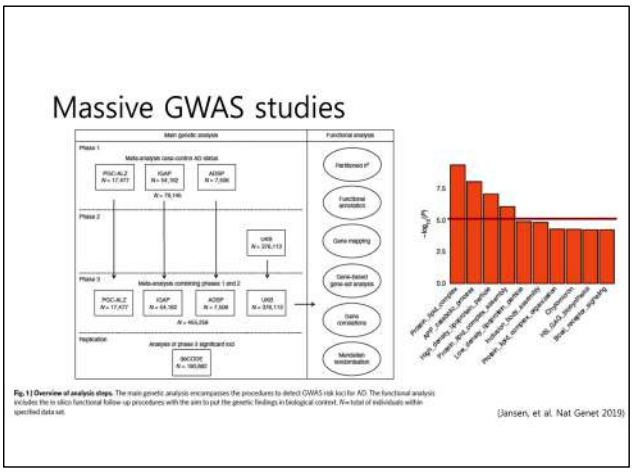


Fig. 1 | Overview of analysis steps. The main genetic analysis encompasses the procedures to detect GWAS risk loci for AD. The functional analysis includes the in silico functional follow-up procedures with the aim to put the genetic findings in biological context. N= total of individuals within specified data set.

(Jansen, et al. Nat Genet 2019)

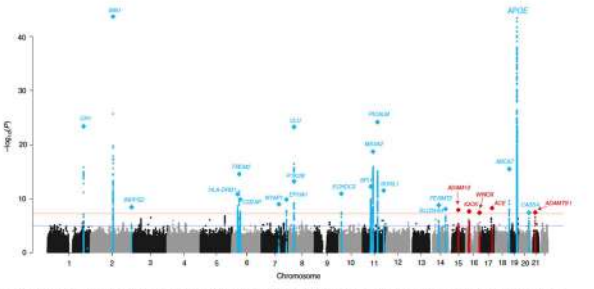
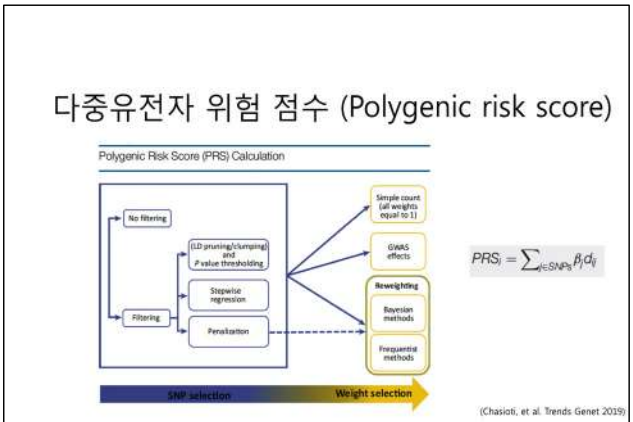


Fig. 1 | Manhattan plot of meta-analysis of Stage 1, 2, and 3 results for genome-wide association with Alzheimer's disease. The threshold for genome-wide significance ($P < 5 \times 10^{-8}$) is indicated by the red line, while the blue line represents the suggestive threshold ($P < 1 \times 10^{-5}$). Loci previously identified by the Lambert et al.' IGAP GWAS are shown in blue and newly associated loci are shown in red. Loci are named for the closest gene to the sentinel variant for each locus. Diamonds represent variants with the smallest *P* values for each genome-wide locus.

(Kunkle, et al. Nat Genet 2019)



(Chasioti, et al. Trends Genet 2019)

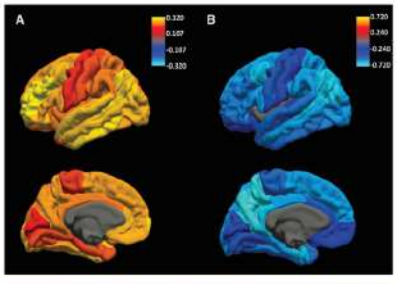


Figure 2 PHS is associated with regional amyloid accumulation and cortical atrophy. Beta estimates of (**A**) cross-sectional associations of PHS with regional florbetapir SUVRs. (**B**) Longitudinal change in regional cortical volumes in individuals with high (1 SD above mean, ~84 percentile) PHS.

(Tan, et al. Brain 2019)

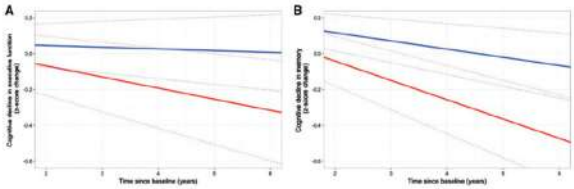
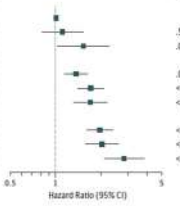


Figure 3 PHS is associated with cognitive and clinical decline beyond imaging markers. Differences in rate of decline in (**A**) executive function, (**B**) memory, (**C**) clinical dementia sum-of-boxes (CDR-SB) over time for low (1 SD below mean, at ~16 percentile; blue lines) and high (1 SD above mean, at ~84 percentile; red lines) PHS non-demented individuals, after accounting for the effects of frontal florbetapir deposition, entorhinal cortex volume, APOE ε4 carrier status, age, sex, and education. Dashed lines are estimated standard error.

(Tan, et al. Brain 2019)

Risk of Incident Dementia According to Genetic and Lifestyle Risk

Subgroup	Total No. of Participants	No. of Cases of Dementia/ Person-Years	Hazard Ratio (95% CI)	P Value
Low genetic risk				
Favorable lifestyle	26 856	151/211 986	1 [Reference]	
Intermediate lifestyle	9114	57/72 342	1.11 (0.81-1.52)	.53
Unfavorable lifestyle	3165	29/24 460	1.52 (1.02-2.26)	.04
Intermediate genetic risk				
Favorable lifestyle	80 290	635/633 405	1.36 (1.14-1.63)	.001
Intermediate lifestyle	27 703	280/219 777	1.70 (1.39-2.08)	<.001
Unfavorable lifestyle	9603	99/74 005	1.70 (1.31-2.19)	<.001
High genetic risk				
Favorable lifestyle	26 407	298/208 769	1.95 (1.60-2.38)	<.001
Intermediate lifestyle	9380	111/74 652	2.02 (1.57-2.58)	<.001
Unfavorable lifestyle	3373	60/26 039	2.83 (2.09-3.83)	<.001



(Lourida, et al. JAMA 2019)

Table 4. Risk of Incident Dementia According to Healthy Lifestyle Category Within Each Genetic Risk Category[a]

Healthy Lifestyle Category[b]	Low			Intermediate			High		
	Favorable (n = 26 856)	Intermediate (n = 9114)	Unfavorable (n = 3165)	Favorable (n = 80 290)	Intermediate (n = 27 703)	Unfavorable (n = 9603)	Favorable (n = 26 407)	Intermediate (n = 9380)	Unfavorable (n = 3373)
No. of dementia cases/person-years[b]	151/211 986	57/72 342	29/24 460	635/633 405	280/219 777	99/74 005	298/208 769	111/74 652	60/26 039
HR (95% CI)	0.69 (0.46-1.04)	0.75 (0.48-1.19)	1 [Reference]	0.80 (0.65-0.99)	1.00 (0.79-1.26)	1 [Reference]	0.68 (0.51-0.90)	0.71 (0.51-0.97)	1 [Reference]
P value	.07	.22		.04	1.00		.008	.03	
P value for trend	.11			.003			.03		

Abbreviation: HR, hazard ratio.

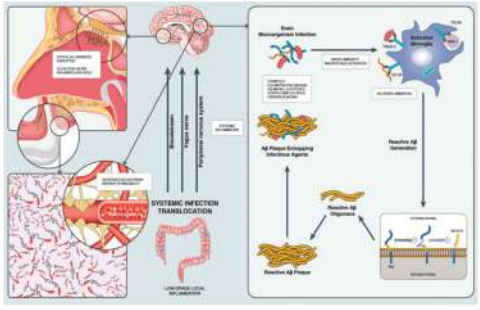
[a] Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, and first 20 principal components of ancestry.

(Lourida, et al. JAMA 2019)

Pathophysiology

치매는 왜 생기나요?

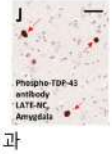
Hypothetical process by which brain infection may lead to Aβ plaque deposition



(Panza, et al. Brain 2019)

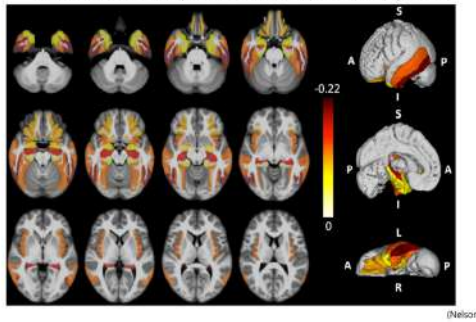
LATE (Limbic-predominant age-related TDP-43 encephalopathy)

- 지역사회 부검 연구 결과 80세 이상에서 >20% (50% 까지도 보고)
- 기억 저하 위주의 인지 장애
- 알츠하이머병(AD) 등 타 퇴행성 질환과 흔히 동반
- Pure AD 보다 내측두부 위축 더 심하나 완만한 임상 경과

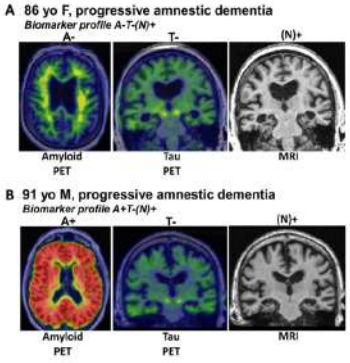


(Nelson, et al. Brain 2019)

Brain atrophy associated with autopsy-confirmed LATE-NC: Data from Rush University ROS-MAP community-based autopsy cohorts



(Nelson, et al. Brain 2019)



(Nelson, et al. Brain 2019)

Summary

- Treatment
  - ✓주된 흐름은 Anti-Aβ 약제이고 대부분 실패하였으나 희망은 있음
- Genetics
  - ✓전통적인 강자(*APOE*)를 추격하는 GWAS/PRS
- Pathophysiology
  - ✓감염/염증에 주목
  - ✓LATE