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A Brief Synopsis on the Genetics of Alzheimer's Disease

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Alzheimer's disease (AD) is the most common form of dementia, accounting for 60–80% of all dementia cases [1]. Due to variation in age at onset (AAO), AD is classified as either early onset (AAO < 60 years) or late onset (AAO ≥ 60 years). Approximately 5% of all AD cases are classified as early-onset AD (EOAD) [2], of which 10–15% having the family history of disease follow the autosomal dominant inheritance [3] with known mutations in three genes: *APP*, *PSEN1*, and *PSEN2* [4]. Majority of the remaining EOAD cases are sporadic with a complex genetic etiology.

Late-onset AD (LOAD) that comprises about 95% of all AD cases is genetically even more complex with polygenic risk inheritance. LOAD has a substantial genetic component with heritability estimates up to 79% [5]. Until recently, *APOE* was the only established susceptibility gene for LOAD. Substantial progress has been made via large-scale genome-wide association studies (GWAS) as well as meta-analyses of GWAS that have identified more than 30 susceptibility loci for LOAD [6–14], mostly among populations of European ancestry. However, known common polymorphisms at these loci explain 16% of the AD phenotypic variance (or 31% of genetic variance) [15]. Recent application of whole-exome microarray, whole-exome sequencing, whole-genome sequencing, and targeted sequencing has identified rare variants in additional novel LOAD genes [16–24].

The purpose of this brief synopsis is to provide an update on the known number of AD genes and loci that have been independently replicated or meet stringent criteria of genome-wide significance (Table 1). In addition to the three causal genes for autosomal dominant EOAD, to date, 43 susceptibility genes/loci have been identified for LOAD. The *APP* gene for EOAD also harbors a protective variant for LOAD. This list of genes will need to be amended as more genes/loci are discovered and GWAS-implicated loci are refined to identify specific genes. Unlike *APOE* and those LOAD genes where the sequencing approach has revealed rare and coding AD-associated variants, the identity of specific genes driving the associations within most GWAS-implicated loci is not known. Functional follow-up of these genetic loci in in vitro and/or in vivo studies will help to identify the specific genes and their relevance to AD pathology.

The ultimate goal of understanding the complete genetic architecture of AD is to discover novel pathways that may converge in the causation of this heterogeneous disease, and to identify drug targets for therapeutic treatment. Manually curated pathways based on a selected set of probable LOAD genes provide some insights about possible disease mechanisms [25], but without including the products (proteins) of all known genuine and yet to be discovered AD genes (both for early and late onset), and those interacting with these genes/proteins, the interpretation of these pathways is incomplete.

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Table 1 AD-associated genes/loci

Chromosome	Region	Gene/locus	Variant frequency	Variant effect	Reference
Autosomal dominant genes					
1	1q42.13	PSEN2	Rare	Risk	[4]
14	14q24.2	PSEN1	Rare	Risk	[4]
21	21q21.3	APP	Rare	Risk	[4]
LOAD susceptibility genes					
4	4q23	UNC5C	Rare	Risk	[21]
6	6p21.1	TREM2	Rare	Risk	[17, 23]
7	7q21.2	AKAP9[1]	Rare	Risk	[22]
7	7q	AC099552.4*	Rare	Risk	[23]
15	15q21.3	ADAM10	Rare/common	Risk/protective	[7, 24]
15	15q26.3	TM2D3	Rare	Risk	[20]
16	16q24.1	PLCG2	Rare	Protective	[19]
17	17q21.32	ABI3	Rare	Risk	[19]
19	19q13.32	APOE	Common	Risk/protective	[6–9]
19	19q13.2	PLD3	Rare	Risk	[18]
21	21q21.3	APP	Rare	Protective	[16]
LOAD susceptibility loci					
1	1q32.2	CR1	Common	Risk	[6, 7]
2	2q37.1	INPP5D/SHIP1	Common	Risk	[6, 7]
5	5q31.3	HBEGF/PFDN1[2,3]	Common	Risk	[11, 13]
5	5q14.3	MEF2C/TMEM161B	Common	Protective	[6]
6	6p12.3	CD2AP/ADGRF2	Common	Risk	[6–9]
6	6p21.32	HLA-DRB1/HLA-DQB1	Common	Risk	[6, 7]
7	7p12.1	COBL[1]	Rare	Protective	[10]
7	7p14.1	NME8/EPDR1	Common	Protective	[6]
7	7q22.1	NYAP1/PILRA/STAG3	Common	Protective	[6, 7, 23]
7	7q34-q35	EPHA1/TAS2R60	Common	Protective	[6, 7]
8	8p21.2	PTK2B	Common	Risk	[6, 7]
8	8p21.2	CLU/APOJ	Common/rare	Risk/protective	[6, 7]
10	10p14	ECHDC3/USP6NL[2,3]	Common	Risk	[7, 11, 13]
11	11p11.2	SPI1/CELF1	Common	Risk/protective	[6, 7]
11	11q12.1	MS4A2/MS4A6A	Common	Protective	[6–9]
11	11q14.2	PICALM	Common	Protective	[6, 7]
11	11q24.1	SORL1	Common/rare	Risk/protective	[6, 7]
13	13q33.1	SLC10A2/METTL21EP[1]	Rare	Protective	[10]
14	14q22.1	FERMT2	Common	Risk	[6, 7]
14	14q32.12	SLC24A4/RIN3	Common	Protective	[6, 7]
15	15q21.2	SPPL2A/TRPM7[3]	Common	Protective	[13]
15	15q22.31	TRIP4	Rare	Risk	[14]
16	16p12.3	IQCK/DEF8	Common	Protective	[7]
17	17p13.2	SCIMP/ZNF594/USP6[3]	Common	Protective	[13]
17	17q21.31	KANSL1/MAPT[4]	Common	Protective	[12]
17	17q22	TSPOAP1/BZRAP1-AS1[2]	Common	Protective	[11]
17	17q23.3	ACE	Rare	Risk	[7]
18	18q12.1	DSG2/DSG3	Common	Protective	[6]
19	19p13.3	ABCA7	Rare/common	Risk	[6, 7, 9], [23]
19	19p13.3	NFIC[2,5]	Common	Protective	[11]
19	19q13.41	CD33/SIGLECL1	Common	Protective	[6, 8, 9]
20	20q13.31	CASS4/GSTF1	Common	Protective	[6, 7]
21	21q21.3	ADAMTS1/ADAMTS5	Common	Protective	[7]

*Long non-coding RNA, [1] unique in African blacks, [2] transethnic GWAS, [3] GWAS by proxy (GWAX), [4] GWAS among non-APOE*4, [5] interaction with APOE*4

Compliance with Ethical Standards

Conflict of Interest M. Ilyas Kamboh declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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