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Alzheimer's disease (AD) is a neurodegenerative disorder for which more than 20 genetic loci have been implicated to date. However, studies demonstrate not all genetic factors have been identiýed. Therefore, in this study we seek to identify additional rare variants and novel genes potentially contributing to AD.

Whole exome sequencing was performed on 23 multi-generational families with an average of eight affected subjects. Exome sequencing was ýltered for rare, nonsynonymous and loss-of-function variants. Alterations predicted to have a functional consequence and located within either a previously reported AD gene, a linkage peak (LOD>2), or clustering in the same gene across multiple families, were prioritized.

Rare variants were found in known AD risk genes including *AKAP9*, *CD33*, *CR1*, *EPHA1*, *INPP5D*, *NME8*, *PSEN1*, *SORL1*, *TREM2* and *UNC5C*. Three families had ýve variants of interest in linkage regions with LOD>2. Genes with segregating alterations in these peaks include *CD163L1* and *CLECL1*, two genes that have both been implicated in immunity, *CTNNA1*, which encodes a catenin in the cerebral cortex and *MIEF1*, a gene that may induce mitochondrial dysfunction and has the potential to damage neurons. Four genes were identiýed with alterations in more than one family include *PLEKHG5*, a gene that causes Charcot-Marie-Tooth disease and *THBS2*, which promotes synaptogenesis.

: Utilizing large families with a heavy burden of disease allowed for identification of rare variant genes

Ke d :

I d c

APOE ε4 0

AKAP9, PLD3, TREM2 UNC5C, TREML2 -1

NOTCH3, PLD3. TTC3 ,1 ,1/

APOE ε2. /0

PSEN1 1

Ma e a a d Me h d

Pa e a ce a e fe e ded AD fa e

0

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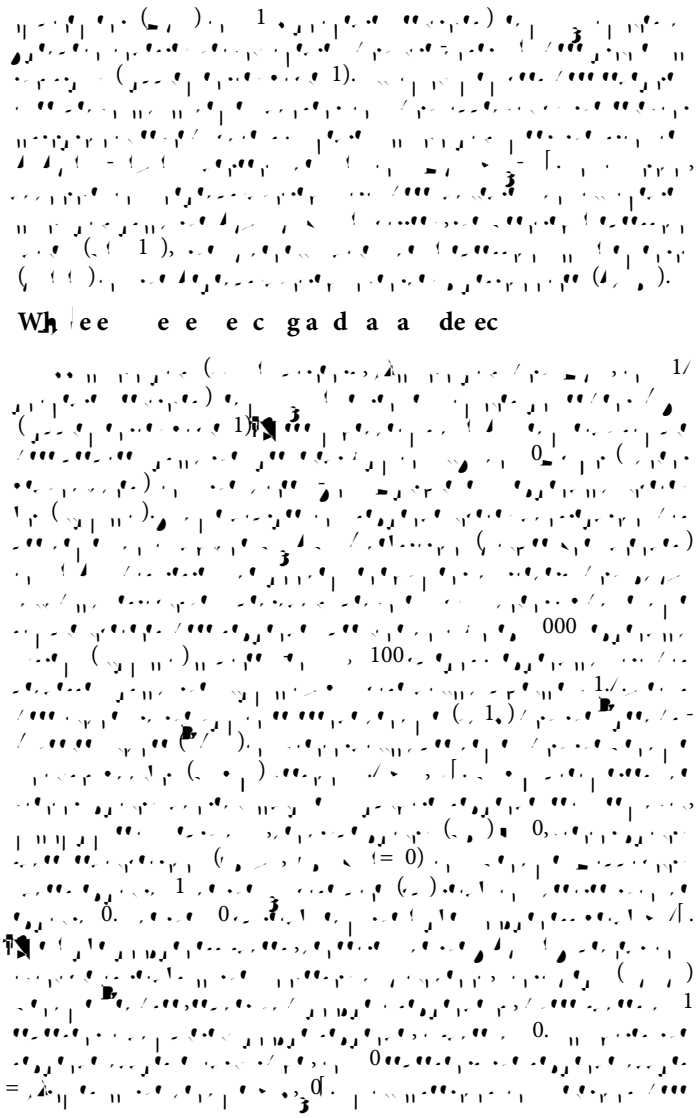

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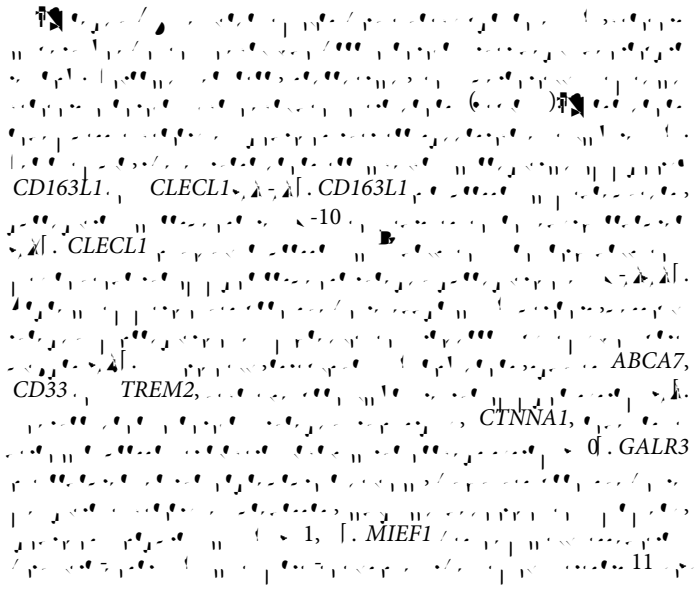

CD163L1 *CLECL1* *CD163L1* -10 *CLECL1* *ABCA7*, *CD33* *TREM2*, *CTNNA1*, *GALR3* 1, *MIEF1*

CD163L1, *CLECL1*, *CTNNA1*, *GALR3*, *MIEF1*, *PLEKHG5* *THBS2*. *AKAP9*, *INPP5D*, *SORL1*, *UNC5C*.

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