**Supplementary Figure 1.** Genes whose expressions are statistically tied to *BDNF* expression in the ARACNe-derived whole brain transcriptional regulatory network. Edges shown are the subset involving BDNF and its immediate neighbors, extracted from a larger network inferred by the ARACNE algorithm from a compendium of 411 mouse whole brain microarrays. Certain transcription factor nodes are colored green.

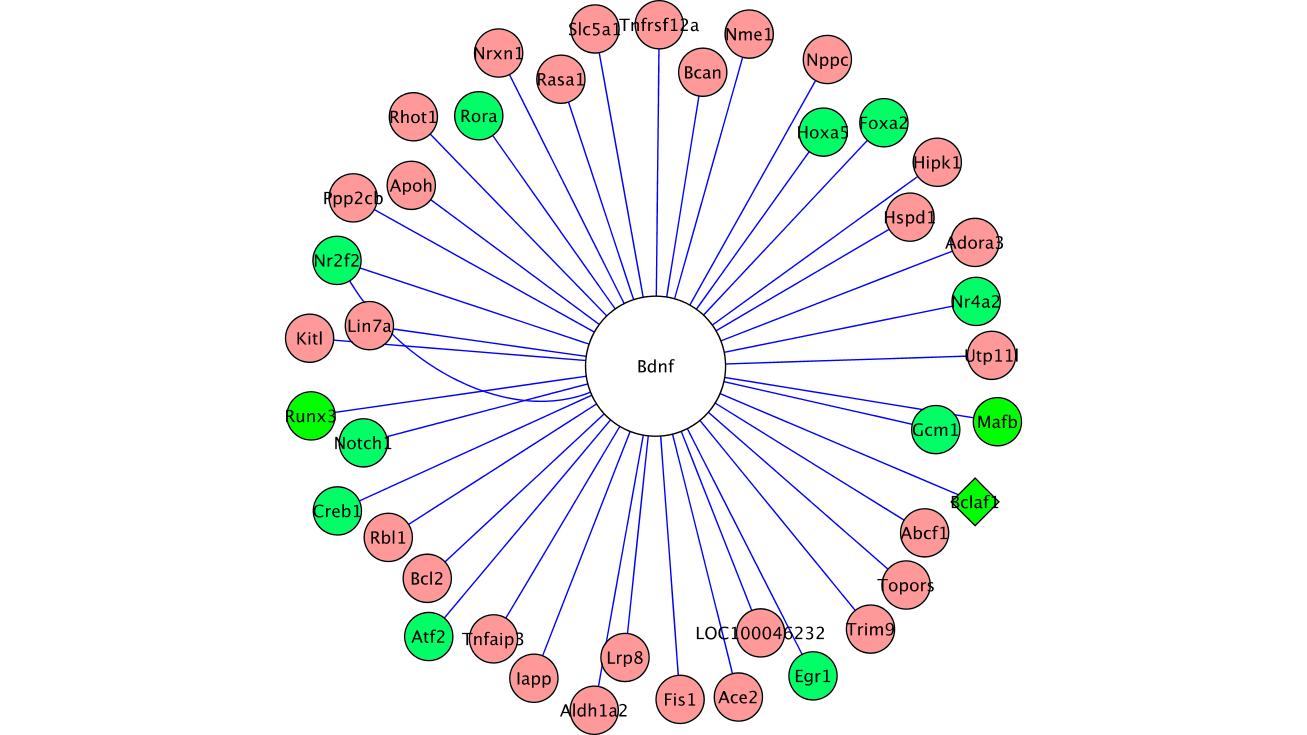
**Supplementary Figure 2.** A top-scoring jActive module from the GENIE3-derived hippocampal network. *RORA* and *RARG* are highlighted in boxes. Also present in this module are several genes discussed in the report including *NFIB, PLXNA2, NR2F1,* and *APP*. Light blue nodes represent genes whose expressions are suppressed in the AD hippocampus; white nodes represent genes whose expressions are elevated in the AD hippocampus. Multiple lines between any given pairs of nodes indicate the genes involved are represented by more than one probe set on the microarray and that the same relationship is detected when alternate probe sets are used.

**Supplementary Figure 3.** An additional top-scoring jActive module from the GENIE3-derived hippocampal network. *RORA* and *RARG* are highlighted in boxes. Also present in this module are several genes discussed in the report including *TIA1, PBX1, GNAQ,* and *APP*. Light blue nodes represent genes whose expressions are suppressed in the AD hippocampus; white nodes represent genes whose expressions are elevated in the AD hippocampus. Multiple lines between any given pairs of nodes indicate the genes involved are represented by more than one probe set on the microarray and that the same relationship is detected when alternate probe sets are used.

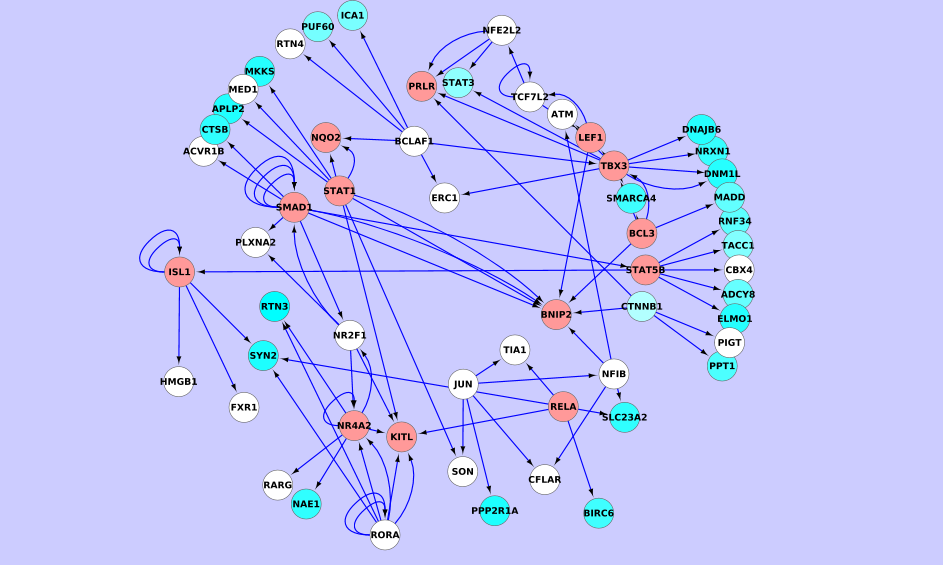
**Supplementary Figure 4.** Genes directly regulated by *RORA* in the GENIE3-derived hippocampal network. Highlighted in boxes are *RORA, IGF1R, IGF1, NR4A2* (via which *RORA* is linked to *RARG* and *INS2),* and *MSX1 (*via which *RORA* is linked to *IGF2).* Light blue nodes represent genes whose expressions are suppressed in the AD hippocampus; white nodes represent genes whose expressions are elevated in the AD hippocampus. Multiple lines between any given pairs of nodes indicate the genes involved are represented by more than one probe set on the microarray and that the same relationship is detected when alternate probe sets are used.

**Supplementary Figure 5.** Genes directly regulated by *NR4A2* in the GENIE3-derived hippocampal network. Highlighted in boxes are *NR4A2, RORA,* and *INS2. NR4A2* links *RORA to RARG* and *INS2*. Light blue nodes represent genes whose expressions are suppressed in the AD hippocampus; white nodes represent genes whose expressions are elevated in the AD hippocampus. Multiple lines between any given pairs of nodes indicate the genes involved are represented by more than one probe set on the microarray and that the same relationship is detected when alternate probe sets are used.

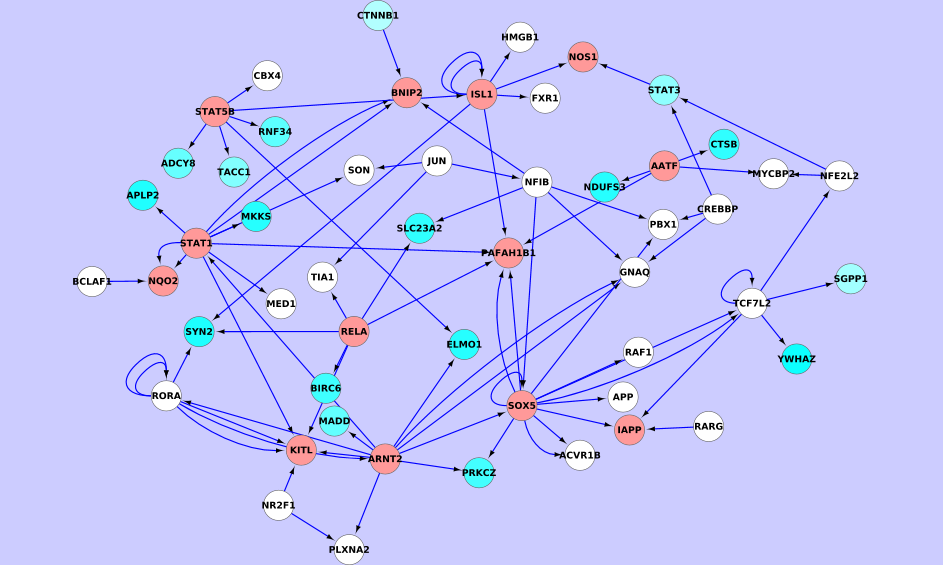
**Supplementary Figure 1**



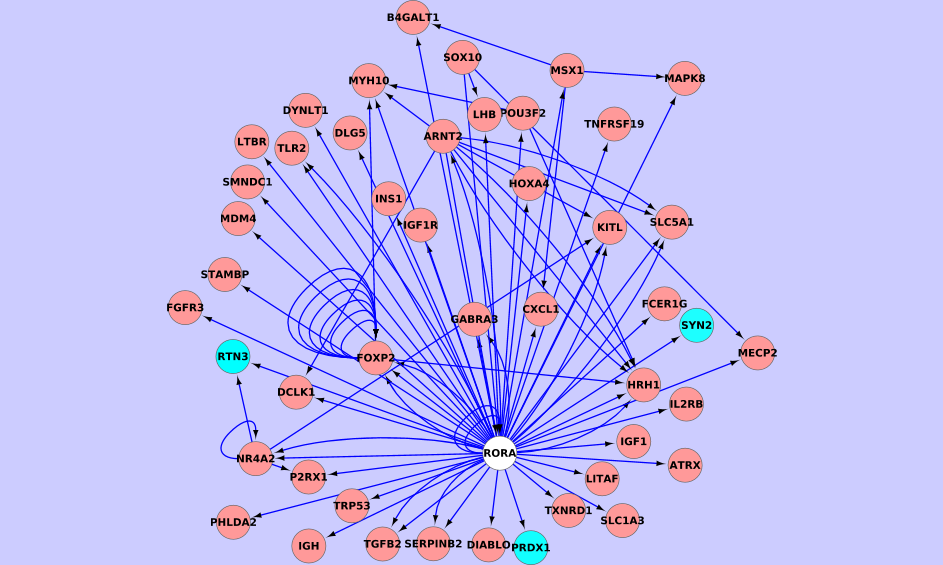
**Supplementary Figure 2**



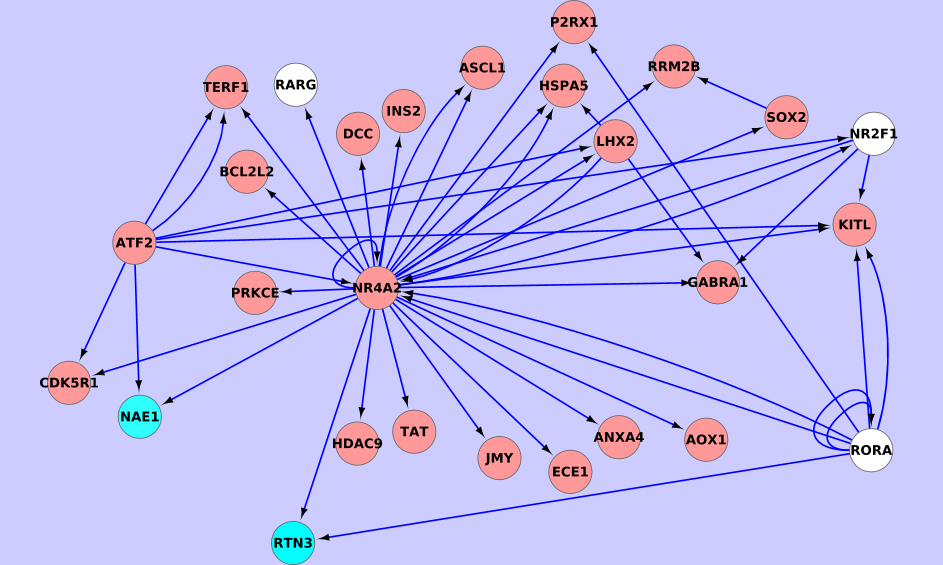
**Supplementary Figure 3**



**Supplementary Figure 4**



**Supplementary Figure 5**



**Supplementary Table 1.** Evidence of involvement of RORA-associated genes/gene products in neurodegeneration/Alzheimer’s disease (AD).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Symbol** | **Name** | **Expression change\*** | **RORA association** | **Neurodegeneration/AD association** | **Reference** |
| DNM1L | Dynamin 1-like | suppressed | jActive Module, MCODE cluster (Figure 1) | Fusion/fission imbalances in the mitochondrion to which DNM1L is linked, associated with AD | [1] |
|  |  |  |  | Nitric oxide-induced S-nitrosylation of DNM1L associated with mitochondrial fission, synaptic loss, and neuronal damage | [2] |
|  |  |  |  | Nitric oxide-induced phosphorylation of DNM1L, activates it and recruits it to the mitochondrion | [3] |
| OPA1 | Optic Atrophy 1 (autosomal dominant) | suppressed | MCODE cluster (Figure 1) | a dynamin family member associated with mitochondrial fusion | [1][4] |
|  |  |  |  | loss of OPA1 function associated with mitochondrial fragmentation and diminished expression of mitochondrial respiratory complexes | [5] |
| TIA1 | TIA1 cytotoxic granule-associated RNA binding protein | elevated | MCODE cluster (Figure 1) | Under conditions of cellular stress, TIA1 promotes the aggregation of RNA-binding proteins to form stress granules | [6] |
|  |  |  |  | Mutations in stress granule components have been implicated in multiple neurodegenerative disorders | [7] |
|  |  |  |  | Stress granules positive for TIA1 are strongly associated with phospho- tau formation in a mouse model of AD | [8] |
| PDCD6IP | programmed cell death 6 interacting protein | elevated | jActive Module | expression is increased in a rodent striatal neurogeneration model that captures hallmarks of Huntington's disease | [9] |
|  |  |  |  | in a kainate-induced neurodegeneration model, PDCD6IP expression is induced in such areas as the hippocampal CA3 region and the piriform cortex | [10] |
| PTK2 | protein tyrosine kinase 2 | suppressed | jActive Module | tyrosine-phosphorylated (and activated) in response to amyloid beta peptide accumulation in neurons | [11] |
|  |  |  |  | Amyloid beta accumulation increases association of PTK2 with Fyn, probably modifying Fyn kinase activity | [12] |
|  |  |  |  | Fyn levels are decreased at synapses and increased in neuronal cell bodies where it is associated with neurofibrillary tangles | [13,14] |
| PLXNA2 | plexin A2 | elevated | jActive Module | PLXNA2-/- mice show increased axonal growth and behavioral recovery after injury | [15] |
| NFIB | nuclear factor I/B | elevated | direct link, jActive Module | association between NFIB and amyloid-beta deposition in the cerebral cortex | [16] |
| APP | amyloid beta (A4) precursor protein | elevated | jActive Module | APP itself, independent of its amyloid beta derivative, is of consequence in the AD etiology | [17] |
|  |  |  |  | role in cell death in the brain | [18-20] |
| CADM1 | cell adhesion molecule 1 | elevated | direct link, jActive Module | Mutations in CADM1 have been associated with autism spectrum disorder | [21] |
| BIRC6 | baculoviral IAP repeat containing 6 | suppressed | direct link, jActive Module | an inhibitor of apoptosis, is expressed in human brain cancer cells in which it inhibits anti-cancer drug-induced apoptosis | [22] |
| DAB1 | Dab, reelin signal transducer, homolog 1 (Drosophila) | elevated | jActive Module | DAB1 is part of the signaling process initiated by Reelin, a protein whose expression gets depleted early in the progression towards AD | [23] |
| RTN3 | reticulon 3 | suppressed | jActive Module | RTN3 inhibits the generation of beta-amyloid protein via its interactions with BACE1 | [24] |
| PBX1 | pre-B-cell leukemia homeobox 1 | elevated | jActive Module | PBX1 is essential for retinoic acid synthesis, which is important during neurodevelopment | [25] |
| NRXN1 | neurexin 1 | suppressed | jActive Module | Association studies link NRXN1 with AD | [26] |
|  |  |  |  | also linked with autism spectrum disorders and other neurodevelopmental disorders | [27][28] |
| RABEP1 | rabaptin, RAB GTPase binding effector protein 1 | elevated | jActive Module | RABEP1-specific IgG found in sera of a majority of AD patients but not in healthy subjects | [29] |
| GNAQ | guanine nucleotide binding protein (G protein), q polypeptide | elevated | direct link, jActive Module | Knockout mice lacking this gene have spatial memory deficits | [30] |
| DHCR24 | 24-dehydrocholesterol reductase | suppressed | direct link, jActive Module | DHCR24 is neuroprotective and anti-apoptotic, and is thought to be involved in AD as its expression is suppressed in relevant brain regions | [31-33] |
| NR2F1 | nuclear receptor subfamily 2, group F, member 1 | elevated | jActive Module | associates with RAN-binding protein-2, which when suppressed reduces neuronal apoptosis and oxidative stress | [34] |

\*in AD hippocampus

**Supplementary Table 2.** HEFalMp scores for genes linked to RORA in the ARACNe-derived network.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Gene | Score |  | Gene | Score |
| *RORA* | 1 |  | *ZEB1* | 0.2099 |
| *UNC5C* | 0.8954 |  | *BTG1* | 0.2096 |
| *PRKG1* | 0.8889 |  | *PURB* | 0.2033 |
| *KCNMA1* | 0.8706 |  | *RB1CC1* | 0.2013 |
| *GABRB1* | 0.8604 |  | *RNF130* | 0.1986 |
| *BRAF* | 0.8418 |  | *BCL11B* | 0.1944 |
| *GRIN2B* | 0.8065 |  | *ATRX* | 0.1925 |
| *HTR2C* | 0.757 |  | *ROCK1* | 0.1907 |
| *PLXNA2* | 0.726 |  | *LRP8* | 0.1742 |
| *GABRA2* | 0.7238 |  | *PURA* | 0.1712 |
| *SLC4A4* | 0.708 |  | *PAFAH1B1* | 0.1508 |
| *SCN2A* | 0.7069 |  | *BBS4* | 0.1484 |
| *MBP* | 0.6862 |  | *RABEP1* | 0.1323 |
| *DCLK1* | 0.6757 |  | *PTEN* | 0.1152 |
| *S100B* | 0.6515 |  | *BIRC6* | 0.1125 |
| *CADM1* | 0.6512 |  | *TRIM35* | 0.1106 |
| *NRXN3* | 0.6417 |  | *GNAQ* | 0.104 |
| *CACNA1A* | 0.6381 |  | *GSK3B* | 0.09845 |
| *NEUROD1* | 0.6254 |  | *SP1* | 0.09785 |
| *SYN1* | 0.5962 |  | *BFAR* | 0.09497 |
| *GABRG2* | 0.583 |  | *ACTN4* | 0.08973 |
| *PEG3* | 0.5426 |  | *CSDE1* | 0.07409 |
| *HOXA5* | 0.5308 |  | *DHCR24* | 0.06744 |
| *PRKCA* | 0.5273 |  | *PIK3CA* | 0.0644 |
| *KITLG* | 0.5262 |  | *SLTM* | 0.05668 |
| *OTX2* | 0.4952 |  | *CREB1* | 0.05579 |
| *STK4* | 0.4875 |  | *HIF1A* | 0.05495 |
| *ZEB2* | 0.4813 |  | *SON* | 0.04403 |
| *NFIB* | 0.4781 |  | *BPTF* | 0.03993 |
| *DAB1* | 0.4517 |  | *OPA1* | 0.03775 |
| *NF1* | 0.4391 |  | *MAP3K7* | 0.0354 |
| *PBX1* | 0.4182 |  | *PPP3CB* | 0.03256 |
| *GABRA4* | 0.4148 |  | *BCLAF1* | 0.02842 |
| *HIPK2* | 0.3859 |  | *SH3GLB1* | 0.0175 |
| *LYST* | 0.3855 |  | *DNM1L* | 0.01542 |
| *FOXO1* | 0.3505 |  | *LIN7C* | 0.01342 |
| *SYT1* | 0.3306 |  | *TIA1* | 0.006623 |
| *LIN7A* | 0.2962 |  | *TXNRD1* | 0.005919 |
| *DIDO1* | 0.2707 |  | *YWHAB* | 0.005709 |
| *PIK3R1* | 0.2627 |  | *CYCS* | 0.00208 |
| *ECE1* | 0.244 |  |  |  |

**Supplementary Table 3.** Analysis of hippocampal differential expression\*\* breakdown between genders.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Both Male and Female** | | **Female Only** | | **Male Only** | |
|  | **Number of Genes** | **Top\* Gene Enrichment Pathways** | **Number of Genes** | **Top\* Gene Enrichment Pathways** | **Number of Genes** | **Top\* Gene Enrichment Pathways** |
| **Increased Expression** | **269** | Nuclear Receptor transcription pathway 3.17E-04 REV-ERBA represses gene expression 3.68E-04 **RORA activates circadian gene expression 4.37E-04** BMAL1:CLOCK,NPAS2 activates circadian gene expression 0.002575 Circadian Clock 0.013807 YAP1- and WWTR1 (TAZ)-stimulated gene expression 0.014229 LRR FLII-interacting protein 1 (LRRFIP1) activates type I IFN production 0.025468 Cohesin Loading onto Chromatin 0.038247 Glycogen breakdown (glycogenolysis) 0.03832 Transcriptional regulation of white adipocyte differentiation 0.053043 | **195** | Attenuation phase 0.003885 Regulation of HSF1-mediated heat shock response 0.008709 HSF1-dependent transactivation 0.008709 HSF1 activation 0.016095 Regulation of gene expression in beta cells 0.016864 Translesion synthesis by Pol eta 0.021969 Cellular response to heat stress 0.028274 Repair synthesis for gap-filling by DNA polymerase in TC-NER 0.044462 Repair synthesis of patch ~27-30 bases long by DNA polymerase 0.044462 Regulation of beta-cell development 0.047037 | **1358** | Interleukin-6 signaling 0.011807 Regulation of cytoskeletal remodeling and cell spreading by IPP complex components 0.03422 Caspase-mediated cleavage of cytoskeletal proteins 0.036952 negative regulation of TCF-dependent signaling by DVL-interacting proteins 0.040956 |
| **Decreased Expression** | **718** | Host Interactions of HIV factors 1.76E-04 HIV Infection 5.19E-04 degradation of DVL 7.77E-04 Membrane Trafficking 7.84E-04 S33 mutants of beta-catenin aren't phosphorylated 0.001012 TCF7L2 mutants don't bind CTBP 0.001012 phosphorylation site mutants of CTNNB1 are not targeted to the proteasome by the destruction complex 0.001012 AXIN mutants destabilize the destruction complex, activating WNT signaling 0.001012 APC truncation mutants are not K63 polyubiquitinated 0.001012 Degradation of beta-catenin by the destruction complex 0.001012 | **523** | Regulation of ornithine decarboxylase (ODC) 0.011489 Assembly of the pre-replicative complex 0.018948 Regulation of mRNA stability by proteins that bind AU-rich elements 0.018966 CDT1 association with the CDC6:ORC:origin complex 0.022758 Hedgehog ligand biogenesis 0.026171 Signaling by Hedgehog 0.026171 Processing-defective Hh variants abrogate ligand secretion 0.026171 Autodegradation of Cdh1 by Cdh1:APC/C 0.027056 Regulation of activated PAK-2p34 by proteasome mediated degradation 0.027198 Orc1 removal from chromatin 0.028245 | **2472** | Transport of Mature mRNA derived from an Intron-Containing Transcript 0.04718 RNA Polymerase II Transcription Termination 0.055363 Cleavage of Growing Transcript in the Termination Region 0.055363 |

|  |  |  |
| --- | --- | --- |
| \*sorted by p-values |  |  |
| \*\*postmortem Alzheimer Disease Dataset GSE5281 at a False Discovery Rate of 5% | | |
| (Males with no AD 10, males with AD 6; Females with no AD 3, Females with AD 4) | | |

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