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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Fagan AM, Henson RL, Li Y, et al. Comparison of CSF biomarkers in Down syndrome and autosomal dominant Alzheimer's disease: a cross-sectional study. *Lancet Oncol* 2021; **22:** 615–26.

Appendix

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METHODS

Clinical and cognitive evaluation in adults with DS enrolled in the ABC-DS study

Diagnoses were made using information from core neuropsychological and informant measures (Down Syndrome Mental Status Examination, Extended & Block Design, Verbal Fluency, Berry-Buktenica Test of Visual Motor Integration, Vineland Adaptive Behavior Scale – Third Edition, Dementia Questionnaire for People with Learning Disabilities, Reiss Screen for Maladaptive Behavior), neurological exam, medical history and record review, generally consistent with the recommendations of the AAMR-IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability (Aylward 1997; Burt 2000). Diagnoses were made using a consensus-based procedure. A consensus conference includes at least three individuals with clinical training and expertise in evaluating dementia in adults with DS (e.g., psychologist, physician), each of whom had participated in the clinical assessment of a given participant.

RESULTS

Demographics

Four DS individuals with missing karyotype data were 53, 54, 55 and 56 years old. To approximate the degree of mosaicism in these individuals, we examined their copy number variation data from their GWAS as implemented in the GenomeStudio software, and found that these four individuals were most likely to be trisomic rather than disomic in chromosome 21. We further note that GWAS does not fully distinguish between full trisomy vs. mosaicism. The oldest participant (age 61) had a confirmed full trisomy 21.

CSF biomarker profiles in APP DIAN-MC compared to PSEN1/2 DIAN-MC

Since development of AD in DS is most likely to be due to triplication of *APP*, in exploratory analyses we evaluated the biomarker profiles of *APP* DIAN-MC as a separate group (n=29, 15% of the DIAN-MC cohort) and compared them to the DS and combined *PSEN1/2* DIAN-MC groups (**Supplemental Table 3**). *APP* DIAN-MC (mean±SD age, 42.4±9.6 years; EYO, -4.0±10.6 years) exhibited patterns similar to the combined *PSEN1*/2 DIAN-MC (41.1±8.0 years; EYO, -4.9±9.5 years) group in comparison to DS for most biomarkers, including lower levels of CSF Aβ40, Aβ42, NfL and YKL-40, and similar levels of VILIP-1 and SNAP-25. In contrast to *PSEN1/2* DIAN-MC, *APP* DIAN-MC had lower levels of tTau and pTau181 and higher Aβ42/Aβ40 ratios compared to the DS group. Adjustment for age, *APOE* ε4 status and sex influenced some but not all results. When restricting this exploratory comparison further to include only the four ADAD individuals specifically expressing an *APP* duplication (*APP*dup) (thus more comparable to DS), the ranges of values for Aβ40 and Aβ42 were in the high range (Aβ40: 11,785-16,556 pg/mL; Aβ42: 547-1024 pg/mL), more like the DS (as opposed to the *PSEN1/2* DIAN-MC) group. Missing data prevented comparison of the emerging biomarkers in the full (n=4) *APP*dup group.

Supplemental Table 1. Pairwise comparisons of biomarkers among DS, DIAN-MC and DIAN-NC groups

	DS vs. DIAN-MC			DS vs. DIAN-NC			DIAN-MC vs. DIAN-NC		
Biomarker	**Difference**	**SE**	**p value**	**Difference**	**SE**	**p value**	**Difference**	**SE**	**p value**
Aβ40	4914	510.9	**<.0001**	4484	544.7	**<.0001**	-430	357.2	0.23
Aβ42	342	49.2	**<.0001**	59.7	52.4	0.26	-283	34.4	**<.0001**
Aβ42/Aβ40	0.002	0.004	0.71	-0.02	0.005	**<.0001**	-0.03	0.003	**<.0001**
tTau	90	54.1	0.1	382	57.5	**<.0001**	292	37.1	**<.0001**
pTau181	3.5	10.3	0.74	63.7	11	**<.0001**	60.2	7.2	**<.0001**
tTau/Aβ42	-0.6	0.17	**0.0008**	0.49	0.18	**0.008**	1.1	0.12	**<.0001**
pTau/Aβ42	-0.11	0.03	**0.001**	0.1	0.03	**0.006**	0.21	0.02	**<.0001**
SNAP25	-0.33	0.33	0.31	0.7	0.35	0.07	1	0.25	**0.0002**
VILIP1	18.4	13.6	0.18	63.3	14.7	**<.0001**	44.9	10.6	**<.0001**
YKL40	64.1	15.8	**0.0001**	100	17.1	**<.0001**	36.3	12	**0.003**
logNfL	0.21	0.05	**<.0001**	0.41	0.06	**<.0001**	0.2	0.04	**<.0001**

Comparisons of CSF biomarker levels in the three groups (DS, DIAN-MC and DIAN-NC) in unadjusted models. Linear regressions were used for the comparisons. All p-values were corrected by the Benjamini-Hochberg method (Benjamini and Hochberg 1995). Significant ($p<0.05$) p values are bolded. Abbreviations: Aβ=amyloid-β; ADAD=autosomal dominant Alzheimer disease; DIAN=Dominantly Inherited Alzheimer Network; DS=Down syndrome; DIAN-MC=ADAD mutation carriers; DIAN-NC=ADAD mutation non-carriers; NfL=neurofilament light chain; pTau=pTau181; SE=standard error; SNAP25=synaptosomal-associated protein 25; tTau=total tau; VILIP1=visinin-like protein 1; YKL40=chitinase-3-like protein 1.

Supplemental Table 2. Distribution of specific genetic mutations in the DIAN cohort

PSEN1	**n**	***PSEN1***	**N**	***PSEN2***	**n**	***APP***	**n**
Ala246Glu	1	Leu226Arg	4	Arg62His	1	Asp678His	2
Ala260Gly	15	Leu235Val	3	Arg71Trp	2	Duplication of the entire *APP* gene	6
Ala260Val	2	Leu271Val	6	Asn141Ile	30		
Ala426Pro	8	Leu286Val	2	Leu238Phe	1	Ile716Met	1
Ala431Glu	6	Met139Ile	4	Thr122Pro	1	Ile716Phe	2
Ala79Val	16	Met139Val	1			Ile716Val	4
Arg269His	5	Met146Ile	4			Leu723Arg	2
Arg278Ile	1	Met146Leu	5			Lys670Asn & Met671Leu	4
Asn135Ser	4	Met146Val	2			Val715Ala	1
Asn135Tyr	1	Met233Leu	2			Val717Ile	23
Cys410Tyr	4	Met84Val	1			Val717Leu	1
Cys92Ser	1	Phe105Leu	2			Val717Phe	1
Gln222His	1	Phe105Ser	3			duplication exons 1,2,4,6,12,14, and 16-18-18	1
Glu184Asp	4	Phe176Val	2				
Glu280Ala	1	Phe176del	2				
Glu280Gly	5	Phe283Leu	3				
Gly206Ala	20	Phe386Ser	1				
Gly209Glu	2	Pro264Leu	4				
Gly209Val	1	Pro267Leu	1				
Gly217Arg	3	Ser169Leu	2				
Gly378Glu	1	Ser170Phe	1				
His163Arg	12	Ser178Pro	3				
Ile143Thr	2	Ser212Tyr	3				
Ile168del	1	Ser230Asn	2				
Ile202Phe	1	Ser290Cys	12				
Ile213Leu	1	Thr245Pro	1				
Ile229Phe	2	Tyr115His	2				
Ile238Met	2	Tyr288His	2				
Ile439Val	2	Val261Ile	1				
Intron 4: IVS4+7A>G (het.)	2	Val261Phe	1				
Leu174Arg	2	deletion exon 9	4				
Leu219Pro	2						

Mutation is based on the DIAN family mutation type. Numbers include both mutation carriers (DIAN-MC) and non-carriers (DIAN-NC).

Supplemental Table 3. Prespecified subgroup comparisons of biomarkers among DS, DIAN *PSEN1/2* MC, DIAN *APP* MC and DIAN-NC groups

	PSEN1/2 **DIAN-MC**	***APP*** **DIAN-MC**	**DS**		**Unadjusted model**	**Model adjusted for age, *APOE* ε4 and sex**
Biomarker	**mean (SD), n**	**mean (SD), n**	**mean (SD), n**	**Comparisons**	**p value**	**p value**
Aβ40	8766 (2,712), 163	8318 (3,339), 29	13612 (3892), 41	APP DIAN-MC vs DIAN-NC	0.29	0.16
				APP DIAN-MC vs PSEN DIAN-MC	0.45	0.29
				APP DIAN-MC vs DS	**<0.0001**	**<0.0001**
Aβ42	514 (265), 163	649 (369), 29	877 (287), 41	APP DIAN-MC vs DIAN-NC	**0.007**	**0.004**
				APP DIAN-MC vs PSEN DIAN-MC	**0.019**	**0.010**
				APP DIAN-MC vs DS	**0.0031**	**<0.0001**
Aβ42/Aβ40	0.06 (0.03), 163	0.09 (0.05), 29	0.07 (0.02), 41	APP DIAN-MC vs DIAN-NC	0.56	0.74
				APP DIAN-MC vs PSEN DIAN-MC	**<0.0001**	**<0.0001**
				APP DIAN-MC vs DS	**0.0007**	0.41
tTau	567 (360), 161	476 (370), 27	644 (382), 39	APP DIAN-MC vs DIAN-NC	**0.004**	**0.008**
				APP DIAN-MC vs PSEN DIAN-MC	0.16	0.05
				APP DIAN-MC vs DS	**0.04**	0.28
pTau	94 (73), 161	64 (48), 28	93 (77), 41	APP DIAN-MC vs DIAN-NC	**0.02**	**0.01**
				APP DIAN-MC vs PSEN DIAN-MC	**0.02**	**0.006**
				APP DIAN-MC vs DS	**0.04**	0.66
tTau/Aβ42	1.5 (1.3), 161	1.1 (1.1), 27	0.84 (0.62), 39	APP DIAN-MC vs DIAN-NC	**0.002**	**0.004**
				APP DIAN-MC vs PSEN DIAN-MC	**0.04**	**0.004**
				APP DIAN-MC vs DS	0.36	**0.03**
pTau/Aβ42	0.26 (0.25), 161	0.15 (0.16), 28	0.13 (0.14), 41	APP DIAN-MC vs DIAN-NC	**0.007**	**0.006**
				APP DIAN-MC vs PSEN DIAN-MC	**0.007**	**0.002**
				APP DIAN-MC vs DS	0.7	0.08
SNAP25	4.9 (1.9), 123	4.8 (2.6), 22	4.6 (1.8), 41	APP DIAN-MC vs DIAN-NC	0.09	**0.006**
				APP DIAN-MC vs PSEN DIAN-MC	0.85	0.76
				APP DIAN-MC vs DS	0.85	**0.01**
VILIP1	183 (80), 124	187 (97), 22	202 (92), 41	APP DIAN-MC vs DIAN-NC	**0.03**	**0.01**
				APP DIAN-MC vs PSEN DIAN-MC	0.8	0.68
				APP DIAN-MC vs DS	0.71	0.68
YKL40	185 (79), 124	196 (101), 22	251 (127), 38	APP DIAN-MC vs DIAN-NC	**0.04**	**0.003**
				APP DIAN-MC vs PSEN DIAN-MC	0.58	0.41
				APP DIAN-MC vs DS	**0.04**	0.55
logNfL	3.0 (0.3), 92	2.9 (0.3), 17	3.24 (0.27), 41	APP DIAN-MC vs DIAN-NC	0.15	0.09
				APP DIAN-MC vs PSEN DIAN-MC	0.15	0.14

Comparison of CSF biomarker levels in DS versus *PSEN1/2* and *APP* groups in unadjusted and adjusted models. Linear regressions were used for the comparisons. The adjusted models included age, *APOE* ε4 status, sex and the interaction between age and group as covariates For the comparisons from the adjusted model, the mean differences were tested at their corresponding mean ages (age 41.8 for *APP* DIAN-MC vs DIAN-NC; age 41.3 for *APP* DIAN-MC vs *PSEN1/2* DIAN-MC; age 46.1 for *APP* DIAN-MC vs DS). All p-values were corrected by the Benjamini-Hochberg method (Benjamini and Hochberg 1995). Significant ($p<0.05$) p values are bolded.
Abbreviations: Aβ=amyloid-β; *APP*=amyloid precursor protein gene; DS=Down syndrome; DIAN-MC=ADAD mutation carriers; DIAN-NC=ADAD mutation non-carriers; NfL=neurofilament light chain; *PSEN*=presenilin gene; pTau=pTau181; SD=standard deviation; SNAP25=synaptosomal-associated protein 25; tTau=total tau; VILIP1=visinin-like protein 1; YKL40=chitinase-3-like protein 1.

Supplemental Table 4. Prespecified subgroup comparisons of biomarkers among DS, DIAN-NC and DIAN-MC groups

	Unadjusted model						Model controlled for age, *APOE ε4* status and sex				
Biomarker	**Comparison**	**Difference**	**SE**	**tValue**	**p value**	**Biomarker**	**Comparison**	**difference**	**SE**	**tValue**	**p value**
Aβ40	aDS-aMC	5379	633	8.5	**<.0001**	Aβ40	aDS-aMC at age 39.7	4869	796	6.12	**<.0001**
Aβ40	sDS-sMC	3849	852	4.52	**<.0001**	Aβ40	sDS-sMC at age 46.8	4923	1389	3.54	**0.0009**
Aβ40	aDS-NC	5236	634	8.26	**<.0001**	Aβ40	aDS-NC at age 42.6	4873	678	7.18	**<.0001**
Aβ40	aMC-NC	-143	399	-0.36	0.72	Aβ40	aMC-NC at age 39.8	190	397	0.48	0.63
Aβ40	aDS-sDS	2203	970	2.27	**0.04**						
Aβ40	aMC-sMC	672	430	1.56	0.14						
Aβ42	aDS-aMC	341	58	5.92	**<.0001**	Aβ42	aDS-aMC at age 39.7	435	73	5.95	**<.0001**
Aβ42	sDS-sMC	285	77	3.68	**0.0004**	Aβ42	sDS-sMC at age 46.8	391	128	3.06	**0.004**
Aβ42	aDS-NC	161	58	2.78	**0.006**	Aβ42	aDS-NC at age 42.6	201	62	3.22	**0.003**
Aβ42	aMC-NC	-180	36	-4.96	**<.0001**	Aβ42	aMC-NC at age 39.8	-175	36	-4.81	**<.0001**
Aβ42	aDS-sDS	295	88	3.35	**0.001**						
Aβ42	aMC-sMC	240	39	6.14	**<.0001**						
Aβ42/Aβ40	aDS-aMC	-0.005	0.005	-0.96	0.34	Aβ42/Aβ40	aDS-aMC at age 39.7	0.006	0.006	0.86	0.47
Aβ42/Aβ40	sDS-sMC	0.008	0.007	1.14	0.31	Aβ42/Aβ40	sDS-sMC at age 46.8	0.013	0.011	1.14	0.38
Aβ42/Aβ40	aDS-NC	-0.020	0.005	-3.84	**0.0003**	Aβ42/Aβ40	aDS-NC at age 42.6	-0.015	0.005	-2.67	**0.02**
Aβ42/Aβ40	aMC-NC	-0.015	0.003	-4.57	**<.0001**	Aβ42/Aβ40	aMC-NC at age 39.8	-0.017	0.003	-5.42	**<.0001**
Aβ42/Aβ40	aDS-sDS	0.013	0.008	1.67	0.14						
Aβ42/Aβ40	aMC-sMC	0.026	0.003	7.44	**<.0001**						
tTau	aDS-aMC	195	61	3.21	**0.002**	tTau	aDS-aMC at age 39.7	118	79	1.5	0.2
tTau	sDS-sMC	-26	83	-0.31	0.76	tTau	sDS-sMC at age 46.8	88	134	0.66	0.51
tTau	aDS-NC	336	61	5.55	**<.0001**	tTau	aDS-NC at age 42.6	302	67	4.51	**<.0001**
tTau	aMC-NC	141	38	3.76	**0.0004**	tTau	aMC-NC at age 39.8	156	38	4.1	**0.0002**
tTau	aDS-sDS	-137	94	-1.46	0.17						
tTau	aMC-sMC	-358	41	-8.73	**<.0001**						
pTau181	aDS-aMC	14.08	11.13	1.26	0.25	pTau181	aDS-aMC at age 39.7	-16.37	14.18	-1.15	0.37
pTau181	sDS-sMC	1.09	15.00	0.07	0.94	pTau181	sDS-sMC at age 46.8	6.13	24.74	0.25	0.8
pTau181	aDS-NC	42.37	11.16	3.8	**0.0003**	pTau181	aDS-NC at age 42.6	26.57	12.09	2.2	0.09
pTau181	aMC-NC	28.29	7.06	4.01	**0.0002**	pTau181	aMC-NC at age 39.8	31.09	7.11	4.37	**<.0001**
pTau181	aDS-sDS	-62.48	17.05	-3.66	**0.0004**						
pTau181	aMC-sMC	-75.47	7.62	-9.9	**<.0001**						
tTau/Aβ42	aDS-aMC	-0.14	0.18	-0.8	0.42	tTau/Aβ42	aDS-aMC at age 39.7	-0.34	0.23	-1.46	0.22
tTau/Aβ42	sDS-sMC	-1.14	0.24	-4.66	**<.0001**	tTau/Aβ42	sDS-sMC at age 46.8	-1.14	0.39	-2.9	**0.01**
tTau/Aβ42	aDS-NC	0.33	0.18	1.87	0.09	tTau/Aβ42	aDS-NC at age 42.6	0.26	0.20	1.3	0.23
tTau/Aβ42	aMC-NC	0.48	0.11	4.3	**<.0001**	tTau/Aβ42	aMC-NC at age 39.8	0.51	0.11	4.57	**<.0001**
tTau/Aβ42	aDS-sDS	-0.47	0.28	-1.7	0.11						
tTau/Aβ42	aMC-sMC	-1.46	0.12	-12.16	**<.0001**						
pTau/Aβ42	aDS-aMC	-0.04	0.03	-1.07	0.28	pTau/Aβ42	aDS-aMC at age 39.7	-0.09	0.04	-2.04	0.09
pTau/Aβ42	sDS-sMC	-0.19	0.05	-4.11	**0.0001**	pTau/Aβ42	sDS-sMC at age 46.8	-0.22	0.08	-2.88	**0.01**
pTau/Aβ42	aDS-NC	0.05	0.03	1.49	0.16	pTau/Aβ42	aDS-NC at age 42.6	0.03	0.04	0.71	0.57
pTau/Aβ42	aMC-NC	0.09	0.02	4.05	**0.0001**	pTau/Aβ42	aMC-NC at age 39.8	0.09	0.02	4.26	**0.0002**
pTau/Aβ42	aDS-sDS	-0.13	0.05	-2.63	**0.01**						
pTau/Aβ42	aMC-sMC	-0.28	0.02	-12.4	**<.0001**						
SNAP25	aDS-aMC	0.00	0.39	-0.01	1	SNAP25	aDS-aMC at age 39.7	-0.84	0.45	-1.86	0.15
SNAP25	sDS-sMC	-0.62	0.52	-1.19	0.35	SNAP25	sDS-sMC at age 46.8	-0.28	0.78	-0.35	0.87
SNAP25	aDS-NC	0.39	0.39	1.01	0.38	SNAP25	aDS-NC at age 42.6	-0.04	0.39	-0.09	0.93
SNAP25	aMC-NC	0.39	0.27	1.45	0.3	SNAP25	aMC-NC at age 39.8	0.63	0.26	2.46	0.09
SNAP25	aDS-sDS	-0.91	0.58	-1.58	0.3						
SNAP25	aMC-sMC	-1.53	0.30	-5.18	**<.0001**						
VILIP1	aDS-aMC	22.6	16.3	1.38	0.2	VILIP1	aDS-aMC at age 39.7	-8.6	21	-0.42	0.68
VILIP1	sDS-sMC	22.5	21.9	1.03	0.31	VILIP1	sDS-sMC at age 46.8	34.3	36	0.96	0.5
VILIP1	aDS-NC	44.9	16.4	2.74	**0.02**	VILIP1	aDS-NC at age 42.6	28.4	18	1.61	0.3
VILIP1	aMC-NC	22.3	11.4	1.96	0.08	VILIP1	aMC-NC at age 39.8	27.6	12	2.37	0.11
VILIP1	aDS-sDS	-53.9	24.3	-2.22	0.06						
VILIP1	aMC-sMC	-54.0	12.4	-4.36	**0.0001**						
YKL40	aDS-aMC	71.8	18.6	3.85	**0.0003**	YKL40	aDS-aMC at age 39.7	1.6	20.1	0.08	0.94
YKL40	sDS-sMC	62.2	23.9	2.6	**0.01**	YKL40	sDS-sMC at age 46.8	13.1	34.3	0.38	0.84
YKL40	aDS-NC	73.2	18.7	3.92	**0.0003**	YKL40	aDS-NC at age 42.6	38.0	17.5	2.18	0.18
YKL40	aMC-NC	1.5	12.5	0.12	0.91	YKL40	aMC-NC at age 39.8	21.2	11.2	1.89	0.18
YKL40	aDS-sDS	-73.7	27.1	-2.72	**0.01**						
YKL40	aMC-sMC	-83.3	13.5	-6.16	**<.0001**						
logNfL	aDS-aMC	0.28	0.05	5.11	**<.0001**	logNfL	aDS-aMC at age 39.7	0.11	0.06	1.79	0.15
logNfL	sDS-sMC	0.16	0.07	2.24	**0.03**	logNfL	sDS-sMC at age 46.8	0.11	0.10	1.11	0.32

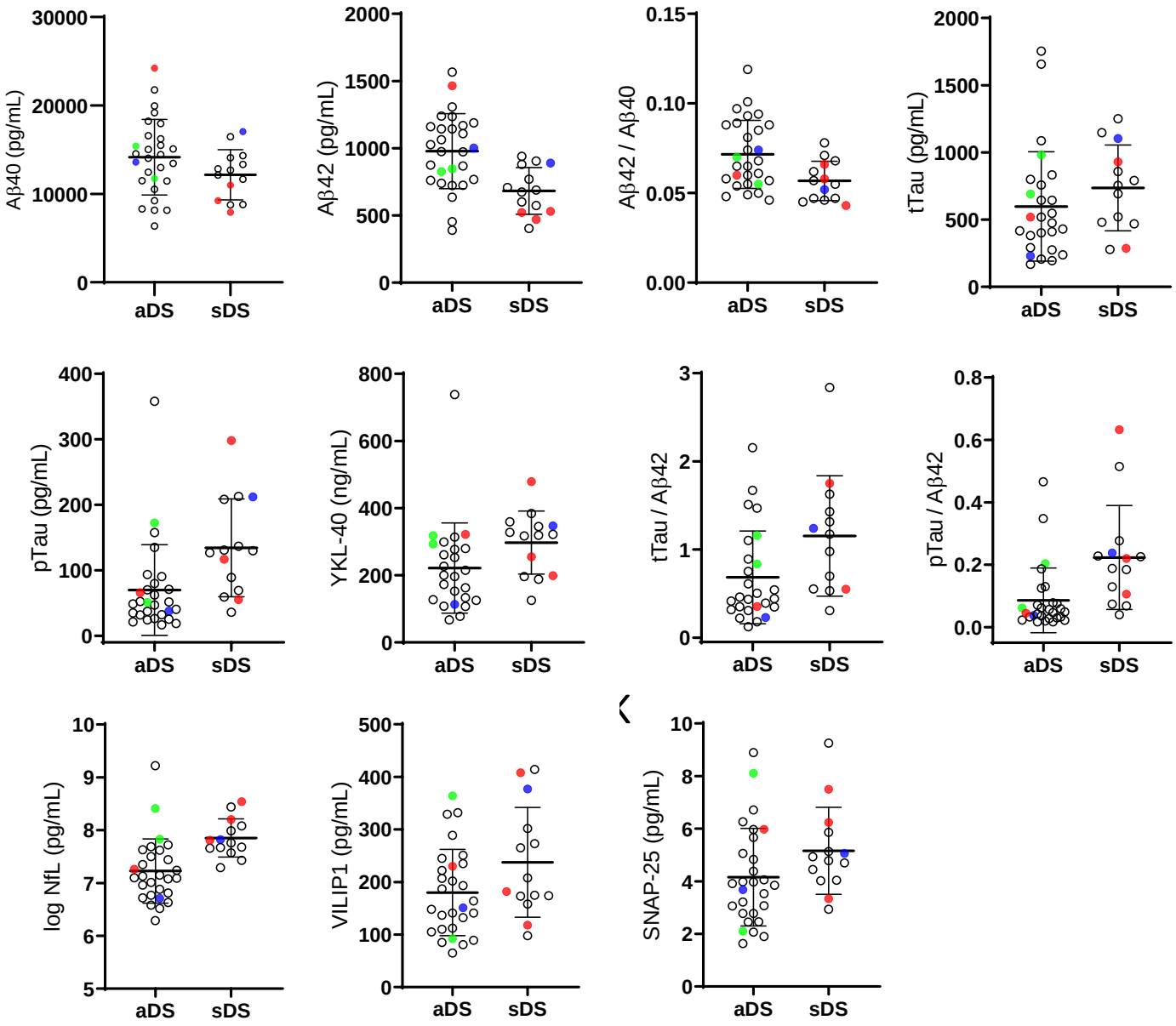
logNfL	aDS-NC	0.32	0.05	5.91	**<.0001**	logNfL	aDS-NC at age 42.6	0.23	0.05	4.44	**<.0001**
logNfL	aMC-NC	0.04	0.04	1.03	0.31	logNfL	aMC-NC at age 39.8	0.10	0.04	2.68	**0.02**
logNfL	aDS-sDS	-0.26	0.08	-3.35	**0.001**						
logNfL	aMC-sMC	-0.38	0.05	-8.22	**<.0001**						

Prespecified subgroup comparisons of CSF biomarker levels in the five subgroups (aDS, sDS, DIAN-NC, DIAN-aMC, DIAN-sMC) in unadjusted and adjusted models. Linear regressions were used to estimate the difference between groups. Age, *APOE* ε4 status, sex and the interaction between age and group were included in the final adjusted model as covariates. Comparisons for aDS versus sDS and DIAN-aMC versus DIAN-sMC were only performed for the unadjusted model since adjustment for covariates was not needed for those comparisons. For the comparisons from the adjusted model, the mean differences were tested at their corresponding mean age (e.g., 39.7 is the mean age of the aDS and DIAN-aMC groups). All p values were corrected by the Benjamini-Hochberg method (Benjamini and Hochberg 1995). Significant ($p<0.05$) p values are bolded. Abbreviations: Aβ=amyloid-β; ADAD; autosomal dominant Alzheimer disease; aDS=asymptomatic DS; CSF=cerebrospinal fluid; DIAN-aMC=asymptomatic DIAN-MC; DIAN-MC=ADAD mutation carriers; DIAN-NC=ADAD mutation non-carriers; DIAN-sMC=symptomatic DIAN-MC; DS=Down syndrome; NfL= neurofilament light chain; sDS=symptomatic DS; SNAP-25=synaptosomal-associated protein 25; tTau=total tau; VILIP1=visinin-like protein 1; YKL40=chitinase-3-like protein 1.

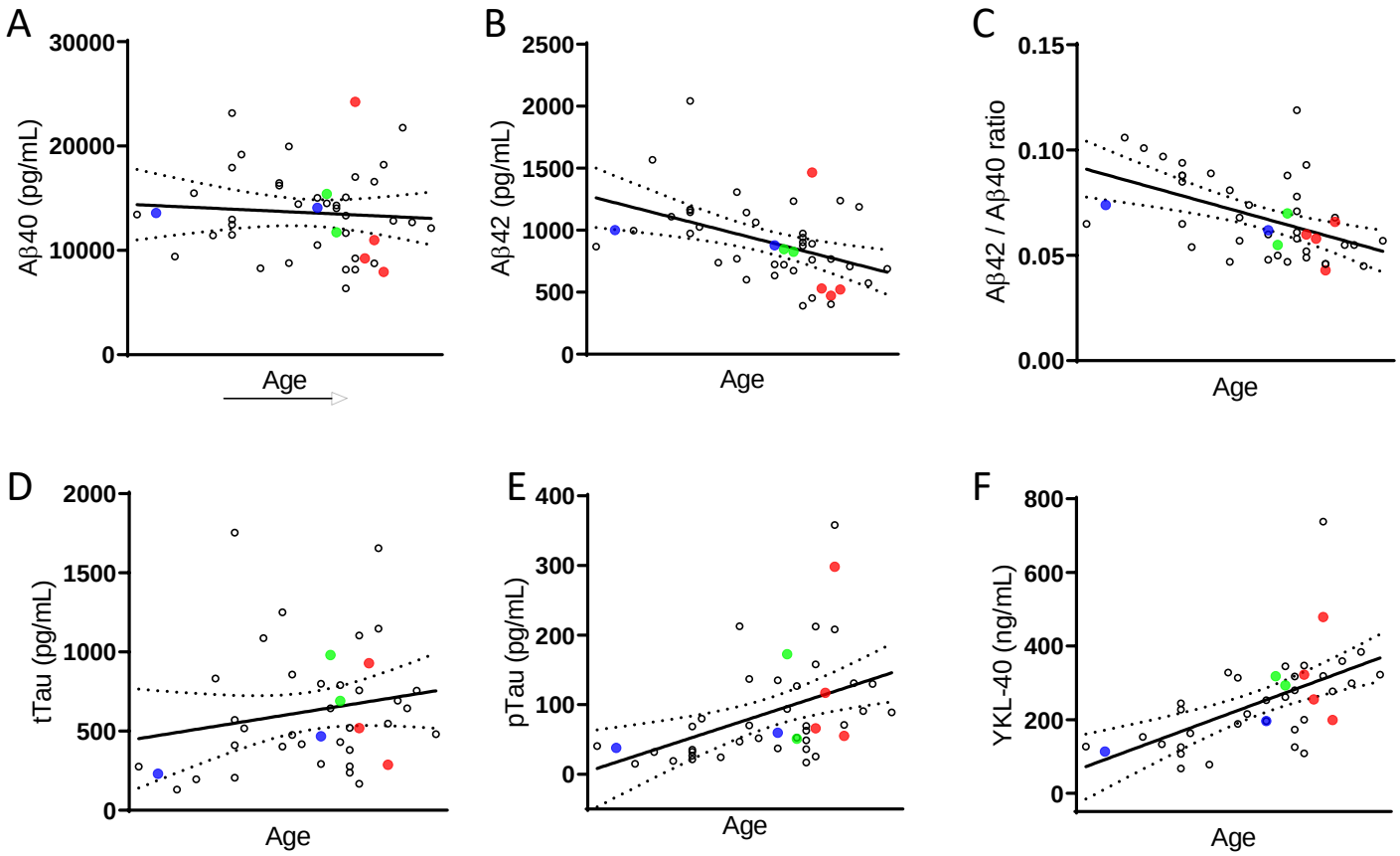
Supplemental Table 5. Pairwise comparisons of annual change in biomarkers by age among DS, DIAN-NC and DIAN-MC groups

	DS vs DIAN-NC			DIAN-MC vs DIAN-NC			DS vs DIAN-MC		
Biomarker	**Difference in slope**	**SE**	**p value**	**Difference in slope**	**SE**	**p value**	**Difference in slope**	**SE**	**p value**
Aβ40	-172.6	71	0.05	-77.7	40.7	0.09	-94.9	68	0.16
Aβ42	-26.9	6.7	**0.0001**	-15.5	3.8	**0.0001**	-11.4	6.4	0.08
Aβ42/Aβ40	-0.001	0.0006	0.12	-0.001	0.0003	**0.003**	0.00009	0.0006	0.88
tTau	7.3	7.3	0.32	15.6	4.1	**0.0006**	-8.3	7	0.32
pTau181	4.3	1.4	**0.003**	2.7	0.79	**0.002**	1.6	1.3	0.23
tTau/Aβ42	0.03	0.02	0.2	0.06	0.01	**<.0001**	-0.03	0.02	0.2
pTau/Aβ42	0.009	0.004	0.05	0.01	0.002	**<.0001**	-0.002	0.004	0.72
SNAP25	0.04	0.04	0.48	0.07	0.03	**0.03**	-0.03	0.04	0.51
VILIP1	3.1	1.9	0.17	1.9	1.2	0.17	1.2	1.8	0.51
YKL40	4.8	1.8	**0.02**	0.7	1.1	0.54	4.1	1.7	**0.03**
logNfL	0.008	0.006	0.28	0.005	0.004	0.28	0.002	0.006	0.67

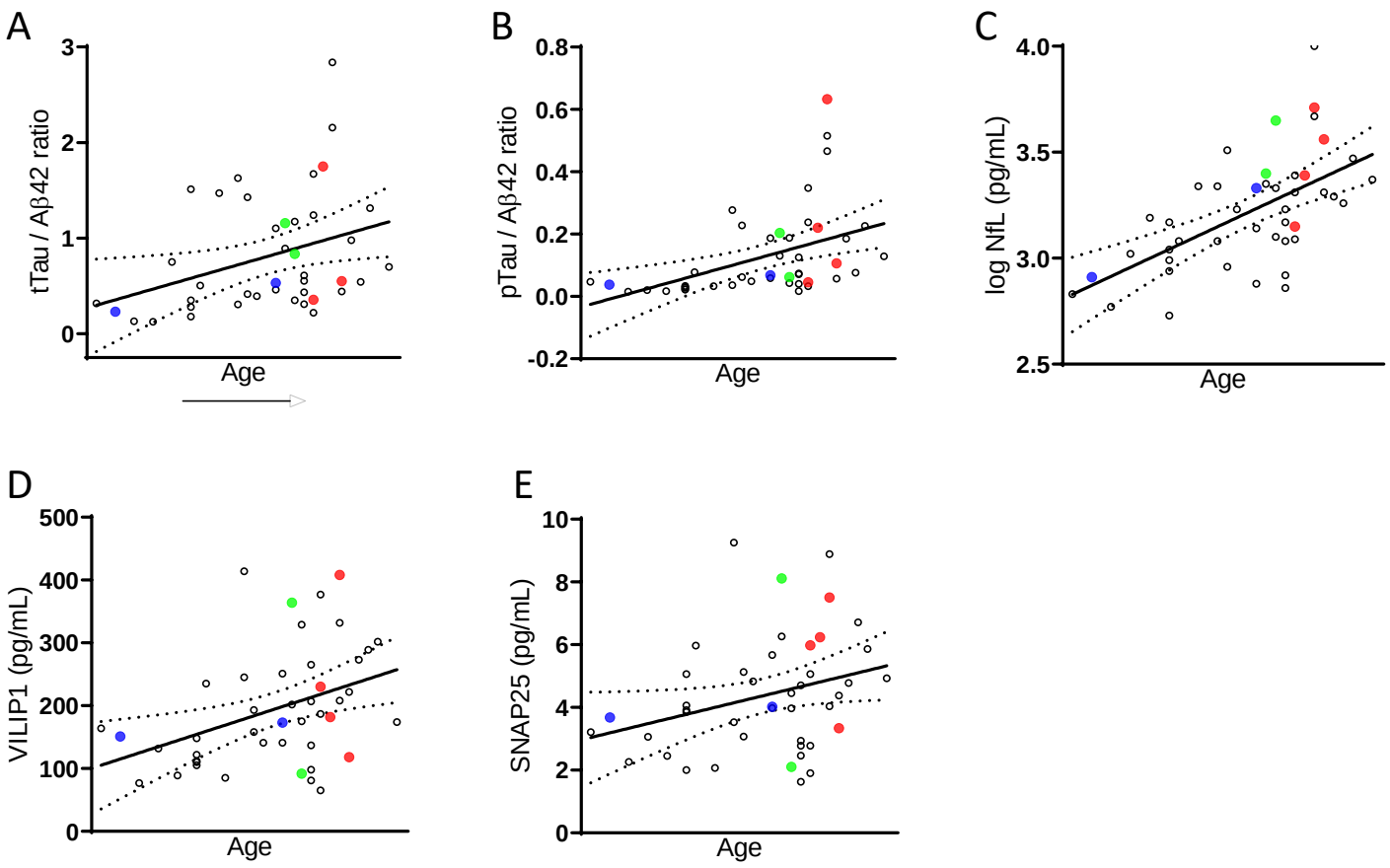
Pairwise comparisons of annual change in biomarker by age among DS, DIAN-NC and DIAN-MC. Linear regressions (biomarker ~ group + age + *APOE* ε4 status + sex + group*age) were used to compare the differences in the annual change in biomarker levels by age among the three groups. All p-values were corrected by the Benjamini-Hochberg method (Benjamini and Hochberg 1995). Significant ($p<0.05$) p values are bolded. Abbreviations: Aβ=amyloid-β; ADAD=autosomal dominant Alzheimer disease; CSF=cerebrospinal fluid; DS=Down syndrome; DIAN-MC=ADAD mutation carriers; DIAN-NC=ADAD mutation non-carriers; NfL=neurofilament light chain; pTau=pTau181; SE=standard error; SNAP25=synaptosomal-associated protein 25; tTau=total tau; VILIP1=visinin-like protein 1; YKL40=chitinase-3-like protein 1.



Supplemental Figure 1. CSF biomarkers in adults with Down syndrome as a function of dementia status and karyotype. Biomarkers include: **A**) Aβ40, **B**) Aβ42, **C**) Aβ42/Aβ40 ratio, **D**) tTau, **E**) pTau181, **F**) YKL-40, **G**) tTau/Aβ42 ratio, **H**) pTau181/Aβ42 ratio, **I**) log transformed NfL, **J**) VILIP-1, and **K**) SNAP-25. The horizontal bar shows the mean concentration, and the vertical lines show the standard deviation. Open circles, trisomy 21 (n=33); Blue, translocation (n=2); Green, mosaicism (n=2); Red, karyotype not available (n=4). Abbreviations: Aβ=amyloid-β; aDS=asymptomatic DS; DS=Down syndrome; NfL, neurofilament light chain; pTau=pTau181; sDS=symptomatic DS; SNAP-25=synaptosomal-associated protein 25; tTau=total tau; VILIP-1=visinin-like protein 1; YKL40=chitinase-3-like protein 1.



Supplemental Figure 2. CSF biomarkers in adults with Down syndrome as a function of age (increasing age left to right) and karyotype. Biomarkers include: **A**) Aβ40, **B**) Aβ42, **C**) Aβ42/Aβ40 ratio, **D**) tTau, **E**) pTau181, and **F**) YKL-40. Actual age is not shown on the X axis in order to maintain blinding. Regression line and 95% confidence intervals (dashed lines) are shown. Open circles, trisomy 21 (n=33); Blue, translocation (n=2); Green, mosaicism (n=2); Red, karyotype not available (n=4). Abbreviations: Aβ=amyloid-β; pTau=pTau181; tTau=total tau; YKL-40=chitinase-3-like protein 1.



Supplemental Figure 3. CSF biomarkers in adults with Down syndrome as a function of age (increasing age left to right) and karyotype. Biomarkers include: A) tTau/Aβ42 ratio, B) pTau/Aβ42 ratio, C) log transformed NfL, D) VILIP-1, and E) SNAP-25. Actual age is not shown on the X axis in order to maintain blinding. Regression line and 95% confidence intervals (dashed lines) are shown. Open circles, trisomy 21 (n=33); Blue, translocation (n=2); Green, mosaicism (n=2); Red, karyotype not available (n=4). Abbreviations: Aβ=amyloid-β; NfL, neurofilament light chain; pTau=pTau181; SNAP-25=synaptosomal-associated protein 25; tTau=total tau; VILIP-1=visinin-like protein 1.

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