

Supplementary Material

Serum neurofilament light chain: A novel biomarker for early diabetic sensorimotor polyneuropathy

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ESM Table 1. List of the 92 biomarkers in the OLINK NEURO EXPLORATORY panel and assay characteristics

Assay	Full name	Uniprot ID	Olink ID	LOD (NPX)	Missing Data freq (% of samples < LOD)	intra-assay (%)	inter-assay (%)	Exclusion
AARSD1	Alanyl-tRNA editing protein Aarsd1	Q9BTE6	OID05202	1.82569	11%	6.05	16.16	
ABHD14B	Protein ABHD14B	Q96IU4	OID05201	0.81444	5%	9.90	33.62	§§
ADAM15	Disintegrin and metalloproteinase domain-containing protein 15	Q13444	OID05162	2.12965	0%	1.15	2.33	
ADGRB3	Adhesion G protein-coupled receptor B3	O60242	OID05521	1.36213	0%	2.25	4.39	
AKT1S1	Proline-rich AKT1 substrate 1	Q96B36	OID05192	0.81980	0%	3.57	8.47	
ANXA10	Annexin A10	Q9UJ72	OID05147	1.42621	0%	2.53	6.97	
AOC1	Amiloride-sensitive amine oxidase (copper-containing)	P19801	OID05212	1.45281	43%	10.63	25.26	§
ASGR1	Asialoglycoprotein receptor 1	P07306	OID05183	0.56951	0%	2.61	5.60	
ATP6V1F	V-type proton ATPase subunit F	Q16864	OID05143	0.77517	57%	15.37	26.25	§
BST2	Bone marrow stromal antigen 2	Q10589	OID05140	1.64665	0%	2.03	3.75	
CARHSP1	Calcium-regulated heat-stable protein 1	Q9Y2V2	OID05198	2.48383	79%	10.04	13.54	§
CCL27	C-C motif chemokine 27	Q9Y4X3	OID05190	0.84066	0%	2.25	3.65	
CD302	CD302 antigen	Q8IX05	OID05152	0.96903	0%	1.36	2.38	
CD33	Myeloid cell surface antigen CD33	P20138	OID05161	0.50305	0%	1.50	6.09	
CD63	CD63 antigen	P08962	OID05222	1.34742	0%	0.82	3.85	
CDH15	Cadherin-15	P55291	OID05134	1.92944	0%	2.48	3.93	
CDH17	Cadherin-17	Q12864	OID05138	0.75868	0%	2.21	4.21	
CEACAM3	Carcinoembryonic antigen-related cell adhesion molecule 3	P40198	OID05164	1.52377	97%	46.05	59.82	§
CETN2	Centrin-2	P41208	OID05133	0.99720	39%	13.06	28.92	§
CLSTN1	Calsyntenin-1	O94985	OID05158	0.56127	9%	8.27	23.99	
COL4A3BP	Collagen type IV alpha-3-binding protein	Q9Y5P4	OID05185	2.00325	13%	5.16	9.92	
CRADD	Death domain-containing protein	P78560	OID05129	1.97500	0%	2.38	5.61	
CRIP2	Cysteine-rich protein 2	P52943	OID05154	3.24357	0%	2.78	5.72	
CTF1	Cardiotrophin-1	Q16619	OID05156	0.87927	95%	NA	NA	§

DEFB4A	Beta-defensin 4A	O15263	OID05200	-1.83046	0%	3.31	5.65	
DPEP1	Dipeptidase 1	P16444	OID05209	2.08402	0%	2.31	5.47	
DPEP2	Dipeptidase 2	Q9H4A9	OID05180	3.02144	1%	4.20	7.98	
DSG3	Desmoglein-3	P32926	OID05170	1.67650	0%	1.63	2.62	
DUSP3	Dual specificity protein phosphatase 3	P51452	OID05204	0.48394	66%	13.76	196.90	§
ECE1	Endothelin-converting enzyme 1	P42892	OID05132	2.27674	90%	10.25	15.97	§
EIF4B	Eukaryotic translation initiation factor 4B	P23588	OID05128	0.86764	0%	3.08	7.30	
EPHA10	Ephrin type-A receptor 10	Q5JZY3	OID05184	1.82915	90%	22.02	21.41	§
EREG	Proepiregulin	O14944	OID05151	1.03308	1%	3.30	6.15	
FCAR	Immunoglobulin alpha Fc receptor	P24071	OID05175	1.09115	0%	3.83	9.57	
FGFR2	Fibroblast growth factor receptor 2	P21802	OID05166	0.43136	0%	2.13	3.69	
FHIT	Bis(5'-adenosyl)-triphosphatase	P49789	OID05157	1.10833	47%	17.90	29.95	§
FKBP5	Peptidyl-prolyl cis-trans isomerase FKBP5	Q13451	OID05220	0.86250	0%	2.42	5.69	
FKBP7	Peptidyl-prolyl cis-trans isomerase FKBP7	Q9Y680	OID05146	1.33611	79%	18.38	31.84	§
FUT8	Alpha-(1.6)-fucosyltransferase	Q9BYC5	OID05195	1.15604	0%	2.38	4.64	
GBP2	Guanylate-binding protein 2	P32456	OID05165	1.96856	98%	18.83	34.64	§
GGT5	Glutathione hydrolase 5 proenzyme	P36269	OID05221	1.68726	0%	1.91	3.64	
GNMB	Transmembrane glycoprotein NMB	Q14956	OID05139	1.49694	0%	0.94	2.34	
GSTP1	Glutathione S-transferase P	P09211	OID05148	1.05669	94%	33.99	78.44	§
HMOX2	Heme oxygenase 2	P30519	OID05207	0.82644	0%	3.54	6.51	
HSP90B1	Endoplasmin	P14625	OID05159	1.41648	90%	24.40	33.22	§
IFI30	Gamma-interferon-inducible lysosomal thiol reductase	P13284	OID05174	-0.27131	0%	2.55	6.03	
IFNL1	Interferon lambda-1	Q8IU54	OID05127	1.92651	89%	18.75	25.45	§
IKZF2	Zinc finger protein Helios	Q9UKS7	OID05178	1.70866	91%	83.40	27.63	§
IL15	Interleukin-15	P40933	OID05169	0.48829	0%	3.64	5.03	
IL32	Interleukin-32	P24001	OID05194	1.43373	0%	2.59	6.03	
IL3RA	Interleukin-3 receptor subunit alpha	P26951	OID05211	0.87502	0%	8.05	16.82	
ILKAP	Integrin-linked kinase-associated serine/threonine phosphatase 2C	Q9H0C8	OID05215	2.35066	47%	6.58	7.39	§
IMPA1	Inositol monophosphatase 1	P29218	OID05153	1.47934	85%	14.06	25.84	§

ING1	Inhibitor of growth protein 1	Q9UK53	OID05217	1.97478	99%	11.42	24.50	§
ISLR2	immunoglobulin superfamily containing leucine-rich repeat protein 2	Q6UXK2	OID05216	1.81788	6%	6.43	12.72	
KIF1BP	KIF1-binding protein	Q96EK5	OID05213	1.79928	11%	4.02	9.16	
KIR2DL3	Killer cell immunoglobulin-like receptor 2DL3	P43628	OID05149	1.14927	17%	5.70	13.48	
KIRREL2	Kin of IRRE-like protein 2	Q6UWL6	OID05188	1.86316	0%	4.45	9.94	
KLB	Beta-klotho	Q86Z14	OID05137	0.79081	0%	2.58	6.03	
LEPR	Leptin receptor	P48357	OID05160	2.01439	0%	1.60	2.96	
LTBP3	Latent-transforming growth factor beta-binding protein 3	Q9NS15	OID05522	1.98197	0%	4.96	8.06	
MAD1L1	Mitotic spindle assembly checkpoint protein MAD1	Q9Y6D9	OID05191	0.52484	0%	3.25	7.62	
NAA10	N-alpha-acetyltransferase 10	P41227	OID05168	2.41388	17%	5.50	9.02	
NDRG1	Protein NDRG1	Q92597	OID05163	1.36602	83%	11.13	24.09	§
NEFL	Neurofilament light polypeptide	P07196	OID05206	1.52833	0%	4.94	6.49	
NPM1	Nucleophosmin	P06748	OID05182	0.87659	0%	1.44	3.36	
NXPH1	Neurexophilin-1	P58417	OID05167	0.88243	86%	21.16	41.82	§
PAEP	Glycodelin	P09466	OID05189	1.21967	47%	20.88	32.98	§
PFDN2	Prefoldin subunit 2	Q9UHV9	OID05197	0.65553	17%	16.21	36.46	§§
PHOSPHO1	Phosphoethanolamine/phosphocholine phosphatase	Q8TCT1	OID05203	1.93143	0%	3.23	8.67	
PLA2G10	Group 10 secretory phospholipase A2	O15496	OID05177	1.71916	0%	2.24	3.77	
PMVK	Phosphomevalonate kinase	Q15126	OID05218	1.35322	0%	3.51	8.25	
PPP3R1	Calcineurin subunit B type 1	P63098	OID05214	0.56858	0%	1.85	3.01	
PRTFDC1	Phosphoribosyltransferase domain-containing protein 1	Q9NRG1	OID05176	2.57623	81%	14.58	18.71	§
PSG1	Pregnancy-specific beta-1-glycoprotein 1	P11464	OID05186	1.08791	3%	3.39	10.23	
PSME1	Proteasome activator complex subunit 1	Q06323	OID05187	0.97657	0%	1.42	4.05	
PTPN1	Tyrosine-protein phosphatase non-receptor type 1	P18031	OID05141	1.53237	0%	2.84	6.24	
PTS	6-pyruvoyl tetrahydrobiopterin synthase	Q03393	OID05193	1.36628	0%	3.31	5.10	
RBKS	Ribokinase	Q9H477	OID05144	0.68171	0%	1.84	4.16	
RNF31	E3 ubiquitin-protein ligase RNF31	Q96EP0	OID05208	1.09796	91%	55.06	48.62	§
RPS6KB1	Ribosomal protein S6 kinase beta-1	P23443	OID05150	1.03833	33%	11.50	21.79	§
SFRP1	Secreted frizzled-related protein 1	Q8N474	OID05171	2.19457	0%	2.89	3.86	

SMOC1	SPARC-related modular calcium-binding protein 1	Q9H4F8	OID05135	0.23440	0%	2.17	4.80	
SNCG	Gamma-synuclein	O76070	OID05210	1.62108	5%	6.50	10.58	
SRP14	Signal recognition particle 14 kDa protein	P37108	OID05142	0.76122	0%	1.60	2.22	
TBCB	Tubulin-folding cofactor B	Q99426	OID05181	1.08991	0%	3.72	6.13	
TDGF1	Teratocarcinoma-derived growth factor 1	P13385	OID05131	1.71268	46%	5.99	9.14	§
TNFRSF13C	Tumor necrosis factor receptor superfamily member 13C	Q96RJ3	OID05205	1.49207	73%	17.37	27.43	§
TPPP3	Tubulin polymerization-promoting protein family member 3	Q9BW30	OID05196	1.34300	40%	12.85	18.90	§
UBE2F	NEDD8-conjugating enzyme UBE2F	Q969M7	OID05179	0.06455	84%	NA	NA	§
VSTM1	V-set and transmembrane domain-containing protein 1	Q6UX27	OID05199	1.12514	6%	6.46	11.21	
WWP2	NEDD4-like E3 ubiquitin-protein ligase	O00308	OID05219	1.83647	0%	2.01	3.74	

Abbreviations: LOD, limit of detection; NA, not applicable (NPX of control measurements below LOD); NPX, normalised protein expression values. NEFL refers to neurofilament light polypeptide or neurofilament light chain or NFL.

The calculation of inter-and intra-assay CVs and the percentage of samples below the LOD was based on measurements of 503 participants recruited consecutively from 2005 to 2011.

§ Excluded from analysis because of missing data for ≥25%.

§§ Excluded from analysis because inter-assay CV >25%

ESM Table 2. Correlations of serum NFL with demographic and metabolic variables

	Non-adjusted correlation		Age-adjusted correlation	
Variable	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age at diagnosis	0.61	<0.0001	-	-
BMI	0.13	0.007	-0.14	0.005
Waist circumference	0.13	0.006	-0.13	0.008
Height	-0.15	0.002	-0.03	0.546
HbA1c	0.05	0.303	0.09	0.049
Total cholesterol	0.13	0.008	-0.05	0.299
eGFR	-0.36	<0.0001	-0.004	0.928

BMI, body mass index; eGFR, estimated glomerular filtration rate

ESM Table 3. Expression levels of 60 neurological biomarkers according to DSPN status

Biomarker	DSPN (n=66)	No DSPN (n=357)
AARSD1	2.3 (2.0, 2.7)	2.3 (2.0, 2.7)
ADAM15	8.8 (8.6, 9.1)	8.8 (8.6, 9.1)
ADGRB3	5.9 (5.6, 6.1)	5.8 (5.6, 6.1)
AKT1S1	2.6 (2.2, 3.1)	2.7 (2.4, 3.0)
ANXA10	2.9 (2.4, 3.3)	2.8 (2.4, 3.6)
ASGR1	4.3 (4.1, 4.7)	4.4 (4.1, 4.6)
BST2	5.8 (5.5, 6.1)	5.8 (5.5, 6.1)
CCL27	5.0 (4.8, 5.3)	5.1 (4.8, 5.3)
CD302	7.2 (6.9, 7.4)	7.1 (6.8, 7.3)
CD33	5.1 (4.2, 5.4)	5.2 (4.3, 5.5)
CD63	8.3 (8.1, 8.6)	8.4 (8.1, 8.6)
CDH15	8.0 (7.2, 8.8)	7.6 (7.0, 8.3)
CDH17	5.9 (5.7, 6.3)	6.0 (5.5, 6.3)
CLSTN1	0.8 (0.6, 1.0)	0.8 (0.7, 1.0)
COL4A3BP	2.3 (2.1, 2.6)	2.4 (2.2, 2.6)
CRADD	4.6 (4.3, 5.0)	4.6 (4.4, 5.2)
CRIP2	5.4 (5.1, 5.6)	5.4 (5.1, 5.6)
DEFB4A	4.9 (3.9, 5.7)	4.6 (3.5, 5.5)
DPEP1	4.0 (3.7, 4.3)	4.0 (3.7, 4.3)
DPEP2	3.8 (3.6, 4.0)	3.8 (3.7, 4.0)
DSG3	6.7 (6.4, 7.0)	6.7 (6.4, 7.0)
EIF4B	4.1 (3.5, 4.7)	4.3 (3.7, 4.8)
EREG	4.5 (4.0, 5.3)	4.6 (4.1, 5.2)
FCAR	2.5 (2.3, 2.8)	2.6 (2.2, 2.9)
FGFR2	5.1 (5.0, 5.2)	5.1 (4.9, 5.3)
FKBP5	4.0 (3.4, 4.5)	4.0 (3.6, 4.6)
FUT8	4.6 (4.3, 5.0)	4.7 (4.4, 5.1)
GGT5	5.7 (5.6, 5.9)	5.7 (5.6, 5.9)
GPNMB	7.9 (7.8, 8.0)	7.9 (7.8, 8.0)
HMOX2	2.9 (2.6, 3.2)	2.9 (2.7, 3.2)
IFI30	3.4 (3.1, 3.8)	3.6 (3.2, 4.0)
IL15	3.4 (3.2, 3.6)	3.3 (3.2, 3.5)
IL32	5.3 (5.2, 5.7)	5.5 (5.2, 5.8)
IL3RA	1.9 (1.7, 2.2)	1.9 (1.6, 2.2)
ISLR2	2.4 (2.0, 2.6)	2.4 (2.2, 2.7)
KIF1BP	2.2 (1.9, 2.6)	2.3 (2.0, 2.6)
KIR2DL3	1.7 (1.4, 2.1)	1.7 (1.3, 2.2)
KIRREL2	2.9 (2.6, 3.0)	2.8 (2.6, 3.0)
KLB	3.6 (3.2, 4.0)	3.6 (3.1, 3.9)
LEPR	5.6 (5.4, 5.8)	5.6 (5.4, 5.8)
LTBP3	3.1 (3.0, 3.4)	3.1 (2.8, 3.4)

Biomarker	DSPN (n=66)	No DSPN (n=357)
MAD1L1	3.1 (2.9, 3.5)	3.2 (2.9, 3.5)
NAA10	2.8 (2.5, 3.3)	2.9 (2.5, 3.3)
NPM1	5.2 (4.7, 5.7)	5.3 (5.0, 5.9)
PHOSPHO1	3.5 (3.3, 3.8)	3.4 (3.2, 3.7)
PLA2G10	5.5 (5.0, 5.9)	5.6 (5.1, 5.9)
PMVK	3.4 (2.9, 3.9)	3.4 (3.0, 4.0)
PPP3R1	3.8 (3.6, 4.1)	3.8 (3.6, 4.0)
PSG1	4.0 (3.4, 4.6)	3.7 (3.1, 4.4)
PSME1	4.2 (4.0, 4.4)	4.2 (4.0, 4.4)
PTPN1	4.8 (4.4, 5.2)	4.8 (4.5, 5.3)
PTS	4.4 (4.0, 4.9)	4.3 (3.9, 5.0)
RBKS	5.9 (5.5, 6.3)	5.8 (5.5, 6.2)
SFRP1	5.7 (5.3, 6.1)	5.5 (5.1, 5.9)
SMOC1	5.1 (4.8, 5.4)	5.0 (4.7, 5.3)
SNCG	2.8 (2.4, 3.2)	2.7 (2.3, 3.2)
SRP14	4.7 (4.1, 5.5)	5.1 (4.5, 5.8)
TBCB	4.0 (3.3, 4.7)	4.2 (3.6, 4.7)
VSTM1	2.0 (1.6, 2.4)	2.0 (1.5, 2.3)
WWP2	4.7 (4.6, 5.2)	4.9 (4.6, 5.3)

Data are expressed as median (25th, 75th percentiles) of NPX values

Biomarkers abbreviations are specified in ESM Table1.

ESM Table 4. Risk ratios (RR) and 95% confidence intervals (CIs) for the associations between neurological biomarkers and prevalent DSPN

	Model 1						Model 2					
	<i>Per 1-NPX</i>			<i>Per 1-SD</i>			<i>Per 1-NPX</i>			<i>Per 1-SD</i>		
Biomarker	RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>
AARSD1	1.13	(0.82, 1.57)	0.462	1.08	(0.88, 1.34)	0.462	1.10	(0.80, 1.53)	0.554	1.07	(0.86, 1.32)	0.554
ADAM15	1.37	(0.79, 2.36)	0.261	1.13	(0.91, 1.41)	0.261	1.47	(0.86, 2.50)	0.159	1.17	(0.94, 1.44)	0.159
ADGRB3	1.01	(0.59, 1.71)	0.976	1.00	(0.82, 1.23)	0.976	1.15	(0.69, 1.92)	0.596	1.06	(0.87, 1.29)	0.596
AKT1S1	1.04	(0.72, 1.50)	0.850	1.03	(0.79, 1.32)	0.85	1.02	(0.71, 1.48)	0.907	1.02	(0.78, 1.31)	0.907
ANXA10	1.04	(0.82, 1.31)	0.754	1.04	(0.83, 1.28)	0.754	1.06	(0.83, 1.35)	0.667	1.05	(0.84, 1.32)	0.667
ASGR1	1.07	(0.53, 2.13)	0.856	1.02	(0.79, 1.33)	0.856	0.82	(0.41, 1.63)	0.573	0.93	(0.72, 1.2)	0.573
BST2	0.98	(0.61, 1.57)	0.922	0.99	(0.8, 1.23)	0.922	0.91	(0.58, 1.45)	0.702	0.96	(0.78, 1.18)	0.702
CCL27	0.94	(0.48, 1.87)	0.870	0.98	(0.77, 1.24)	0.87	1.07	(0.55, 2.10)	0.837	1.02	(0.81, 1.29)	0.837
CD302	1.54	(0.93, 2.55)	0.096	1.19	(0.97, 1.45)	0.096	1.53	(0.93, 2.53)	0.094	1.19	(0.97, 1.45)	0.094
CD33	0.90	(0.73, 1.10)	0.303	0.90	(0.73, 1.1)	0.303	0.95	(0.77, 1.18)	0.658	0.95	(0.77, 1.18)	0.658
CD63	0.84	(0.46, 1.51)	0.556	0.94	(0.77, 1.15)	0.556	0.87	(0.49, 1.55)	0.638	0.95	(0.78, 1.16)	0.638
CDH15	0.96	(0.76, 1.21)	0.709	0.95	(0.75, 1.22)	0.709	0.91	(0.73, 1.14)	0.419	0.91	(0.71, 1.15)	0.419
CDH17	1.24	(0.84, 1.82)	0.284	1.13	(0.9, 1.41)	0.284	1.30	(0.89, 1.91)	0.176	1.16	(0.93, 1.45)	0.176
CLSTN1	0.68	(0.34, 1.38)	0.290	0.83	(0.6, 1.17)	0.29	0.64	(0.31, 1.31)	0.222	0.81	(0.58, 1.14)	0.222
COL4A3BP	0.89	(0.49, 1.63)	0.709	0.96	(0.77, 1.19)	0.709	0.94	(0.52, 1.69)	0.834	0.98	(0.79, 1.21)	0.834
CRADD	1.02	(0.72, 1.44)	0.903	1.01	(0.81, 1.28)	0.903	1.05	(0.75, 1.47)	0.787	1.03	(0.82, 1.29)	0.787
CRIP2	0.80	(0.43, 1.49)	0.489	0.91	(0.7, 1.18)	0.489	0.82	(0.42, 1.62)	0.570	0.92	(0.69, 1.23)	0.570
DEFB4A	1.09	(0.93, 1.27)	0.300	1.12	(0.9, 1.38)	0.3	1.06	(0.91, 1.24)	0.437	1.09	(0.88, 1.33)	0.437
DPEP1	0.95	(0.62, 1.44)	0.804	0.97	(0.79, 1.2)	0.804	1.10	(0.72, 1.69)	0.664	1.05	(0.85, 1.3)	0.664
DPEP2	0.64	(0.30, 1.37)	0.253	0.89	(0.72, 1.09)	0.253	0.72	(0.32, 1.64)	0.435	0.92	(0.73, 1.14)	0.435

	Model 1						Model 2					
	Per 1-NPX			Per 1-SD			Per 1-NPX			Per 1-SD		
Biomarker	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
DSG3	0.79	(0.45, 1.37)	0.398	0.91	(0.72, 1.14)	0.398	0.84	(0.50, 1.42)	0.518	0.93	(0.75, 1.16)	0.518
EIF4B	0.88	(0.68, 1.15)	0.360	0.88	(0.67, 1.15)	0.36	0.93	(0.72, 1.22)	0.613	0.93	(0.71, 1.22)	0.613
EREG	0.98	(0.79, 1.22)	0.855	0.98	(0.79, 1.22)	0.855	0.99	(0.81, 1.22)	0.933	0.99	(0.81, 1.22)	0.933
FCAR	0.94	(0.61, 1.45)	0.779	0.97	(0.80, 1.18)	0.779	0.96	(0.63, 1.47)	0.867	0.98	(0.81, 1.19)	0.867
FGFR2	1.04	(0.49, 2.22)	0.923	1.01	(0.81, 1.25)	0.923	0.85	(0.40, 1.80)	0.670	0.95	(0.77, 1.18)	0.670
FKBP5	0.90	(0.68, 1.19)	0.476	0.92	(0.74, 1.15)	0.476	0.96	(0.72, 1.26)	0.753	0.97	(0.78, 1.20)	0.753
FUT8	0.85	(0.56, 1.30)	0.456	0.92	(0.73, 1.15)	0.456	0.87	(0.57, 1.33)	0.522	0.93	(0.74, 1.17)	0.522
GGT5	1.45	(0.70, 2.98)	0.317	1.11	(0.90, 1.36)	0.317	1.43	(0.73, 2.81)	0.300	1.11	(0.91, 1.34)	0.300
GPNMB	1.24	(0.32, 4.72)	0.755	1.04	(0.83, 1.30)	0.755	1.44	(0.40, 5.21)	0.581	1.06	(0.85, 1.32)	0.581
HMOX2	0.87	(0.55, 1.37)	0.543	0.93	(0.74, 1.18)	0.543	0.89	(0.57, 1.41)	0.621	0.94	(0.74, 1.19)	0.621
IFI30	0.69	(0.44, 1.07)	0.095	0.83	(0.66, 1.03)	0.095	0.65	(0.41, 1.02)	0.059	0.8	(0.64, 1.01)	0.059
IL15	1.27	(0.51, 3.15)	0.608	1.07	(0.83, 1.38)	0.608	1.36	(0.56, 3.30)	0.502	1.09	(0.85, 1.40)	0.502
IL32	1.01	(0.64, 1.59)	0.961	1.01	(0.79, 1.27)	0.961	1.12	(0.73, 1.70)	0.605	1.06	(0.85, 1.32)	0.605
IL3RA	0.84	(0.42, 1.65)	0.609	0.94	(0.74, 1.19)	0.609	0.99	(0.50, 1.97)	0.977	1.00	(0.78, 1.27)	0.977
ISLR2	0.74	(0.42, 1.30)	0.295	0.88	(0.70, 1.12)	0.295	0.79	(0.46, 1.37)	0.406	0.91	(0.72, 1.14)	0.406
KIF1BP	0.99	(0.61, 1.62)	0.983	1.00	(0.79, 1.26)	0.983	1.06	(0.65, 1.74)	0.809	1.03	(0.81, 1.30)	0.809
KIR2DL3	1.01	(0.74, 1.37)	0.970	1.00	(0.81, 1.24)	0.97	1.00	(0.75, 1.35)	0.975	1.00	(0.82, 1.23)	0.975
KIRREL2	1.05	(0.55, 1.99)	0.880	1.02	(0.83, 1.25)	0.88	1.17	(0.62, 2.22)	0.619	1.05	(0.86, 1.29)	0.619
KLB	1.01	(0.71, 1.44)	0.959	1.01	(0.81, 1.25)	0.959	0.99	(0.71, 1.37)	0.946	0.99	(0.81, 1.21)	0.946
LEPR	1.18	(0.53, 2.61)	0.688	1.05	(0.81, 1.37)	0.688	1.82	(0.77, 4.26)	0.171	1.21	(0.92, 1.60)	0.171
LTBP3	1.16	(0.80, 1.68)	0.424	1.08	(0.90, 1.28)	0.424	1.15	(0.76, 1.74)	0.523	1.07	(0.87, 1.30)	0.523
MAD1L1	0.82	(0.49, 1.38)	0.456	0.92	(0.73, 1.15)	0.456	0.88	(0.52, 1.47)	0.618	0.94	(0.75, 1.18)	0.618
NAA10	1.00	(0.69, 1.47)	0.980	1.00	(0.81, 1.24)	0.98	1.08	(0.74, 1.56)	0.690	1.04	(0.85, 1.29)	0.69
NPM1	0.78	(0.55, 1.09)	0.147	0.85	(0.68, 1.06)	0.147	0.83	(0.60, 1.16)	0.273	0.89	(0.71, 1.10)	0.273

	Model 1						Model 2					
	Per 1-NPX			Per 1-SD			Per 1-NPX			Per 1-SD		
Biomarker	RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>
PHOSPHO1	1.49	(0.69, 3.21)	0.307	1.14	(0.88, 1.48)	0.307	1.54	(0.74, 3.21)	0.244	1.16	(0.90, 1.48)	0.244
PLA2G10	0.95	(0.69, 1.30)	0.739	0.96	(0.78, 1.20)	0.739	0.97	(0.66, 1.43)	0.880	0.98	(0.75, 1.28)	0.880
PMVK	0.92	(0.70, 1.22)	0.576	0.94	(0.75, 1.17)	0.576	0.96	(0.74, 1.25)	0.769	0.97	(0.78, 1.20)	0.769
PPP3R1	1.12	(0.48, 2.60)	0.797	1.03	(0.80, 1.33)	0.797	1.05	(0.50, 2.21)	0.894	1.02	(0.81, 1.27)	0.894
PSG1	1.17	(0.92, 1.49)	0.193	1.20	(0.91, 1.57)	0.193	1.20	(0.97, 1.50)	0.095	1.23	(0.96, 1.58)	0.095
PSME1	1.08	(0.64, 1.84)	0.764	1.04	(0.83, 1.30)	0.764	1.05	(0.60, 1.83)	0.872	1.02	(0.80, 1.30)	0.872
PTPN1	0.95	(0.69, 1.31)	0.755	0.97	(0.78, 1.20)	0.755	0.98	(0.72, 1.33)	0.891	0.99	(0.80, 1.21)	0.891
PTS	1.10	(0.83, 1.46)	0.522	1.08	(0.85, 1.37)	0.522	0.96	(0.70, 1.32)	0.823	0.97	(0.75, 1.26)	0.823
RBKS	1.03	(0.71, 1.50)	0.880	1.02	(0.80, 1.30)	0.88	0.92	(0.61, 1.40)	0.707	0.95	(0.73, 1.24)	0.707
SFRP1	1.53	(1.07, 2.20)	0.021	1.30	(1.04, 1.63)	0.021	1.50	(1.01, 2.23)	0.045	1.28	(1.01, 1.64)	0.045
SMOC1	1.40	(0.85, 2.32)	0.189	1.18	(0.92, 1.50)	0.189	1.34	(0.81, 2.24)	0.257	1.15	(0.90, 1.48)	0.257
SNCG	1.19	(0.82, 1.72)	0.372	1.13	(0.86, 1.48)	0.372	1.08	(0.72, 1.62)	0.723	1.05	(0.79, 1.42)	0.723
SRP14	0.81	(0.63, 1.03)	0.087	0.82	(0.65, 1.03)	0.087	0.84	(0.67, 1.06)	0.148	0.85	(0.68, 1.06)	0.148
TBCB	0.96	(0.72, 1.28)	0.782	0.97	(0.75, 1.24)	0.782	0.97	(0.77, 1.21)	0.755	0.97	(0.80, 1.17)	0.755
VSTM1	1.29	(0.90, 1.84)	0.160	1.16	(0.94, 1.42)	0.16	1.28	(0.89, 1.84)	0.185	1.15	(0.94, 1.42)	0.185
WWP2	0.84	(0.51, 1.37)	0.476	0.92	(0.72, 1.17)	0.476	0.91	(0.58, 1.42)	0.678	0.95	(0.77, 1.19)	0.678

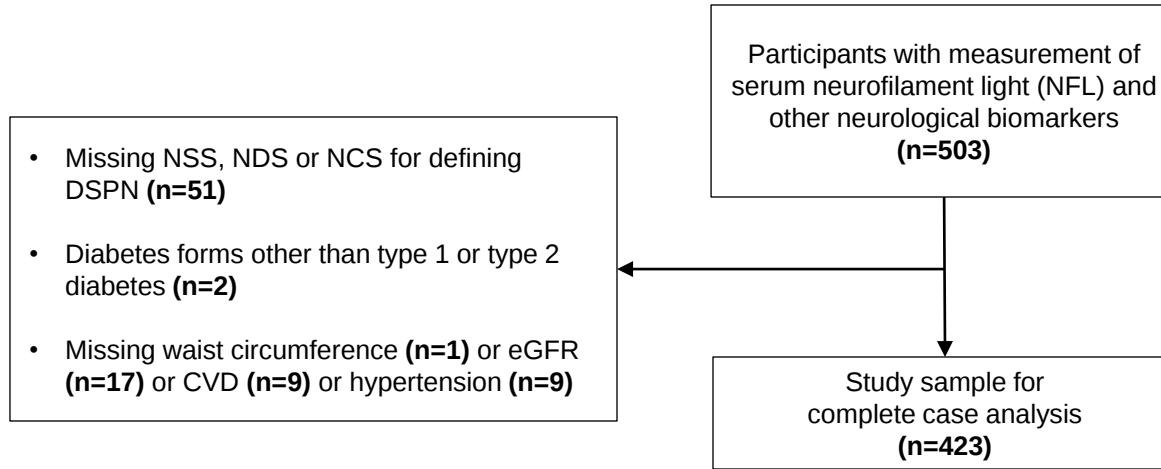
Biomarkers abbreviations are specified in ESM Table 1; CI, confidence interval; DSPN, diabetic sensorimotor polyneuropathy; NPX, Normalized Protein eXpression; RR, risk ratio; SD, standard deviation.

Model 1: adjusted for age and sex.

Model 2: adjusted for model 1+ waist circumference, height, HbA1C, known diabetes duration, diabetes type, eGFR, total cholesterol, hypertension, CVD, use of lipid-lowering drugs and NSAIDs.

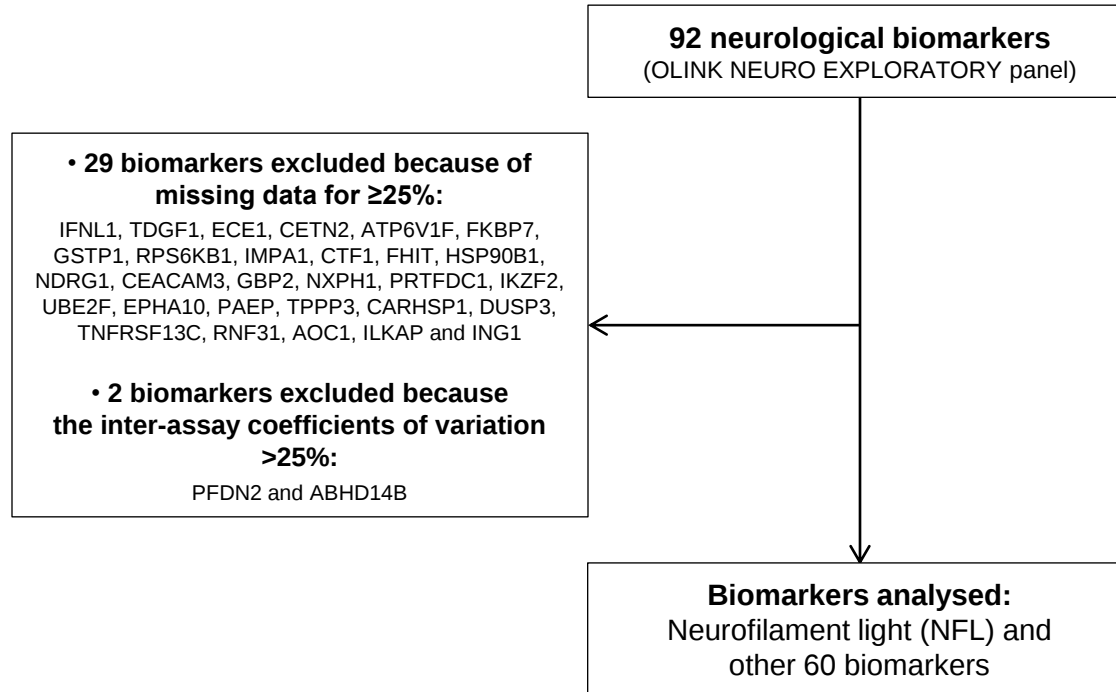
Bonferroni-corrected $p < 0.0008$ indicates significant associations.

ESM Fig.1. Flowchart of the study population

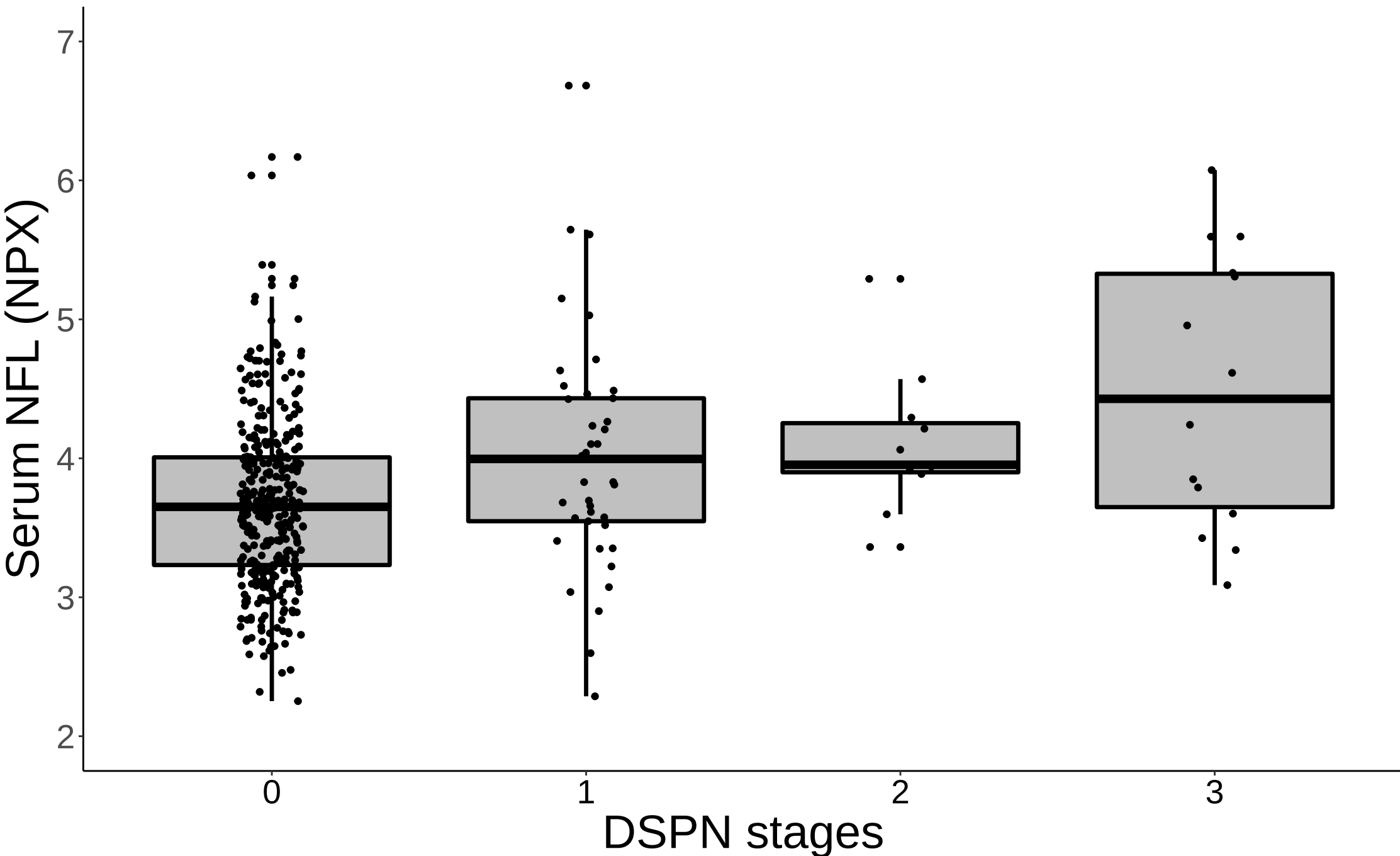


Note: some participants were excluded because of more than one exclusion criterion being applied

ESM Fig.2. Flowchart of biomarkers selection

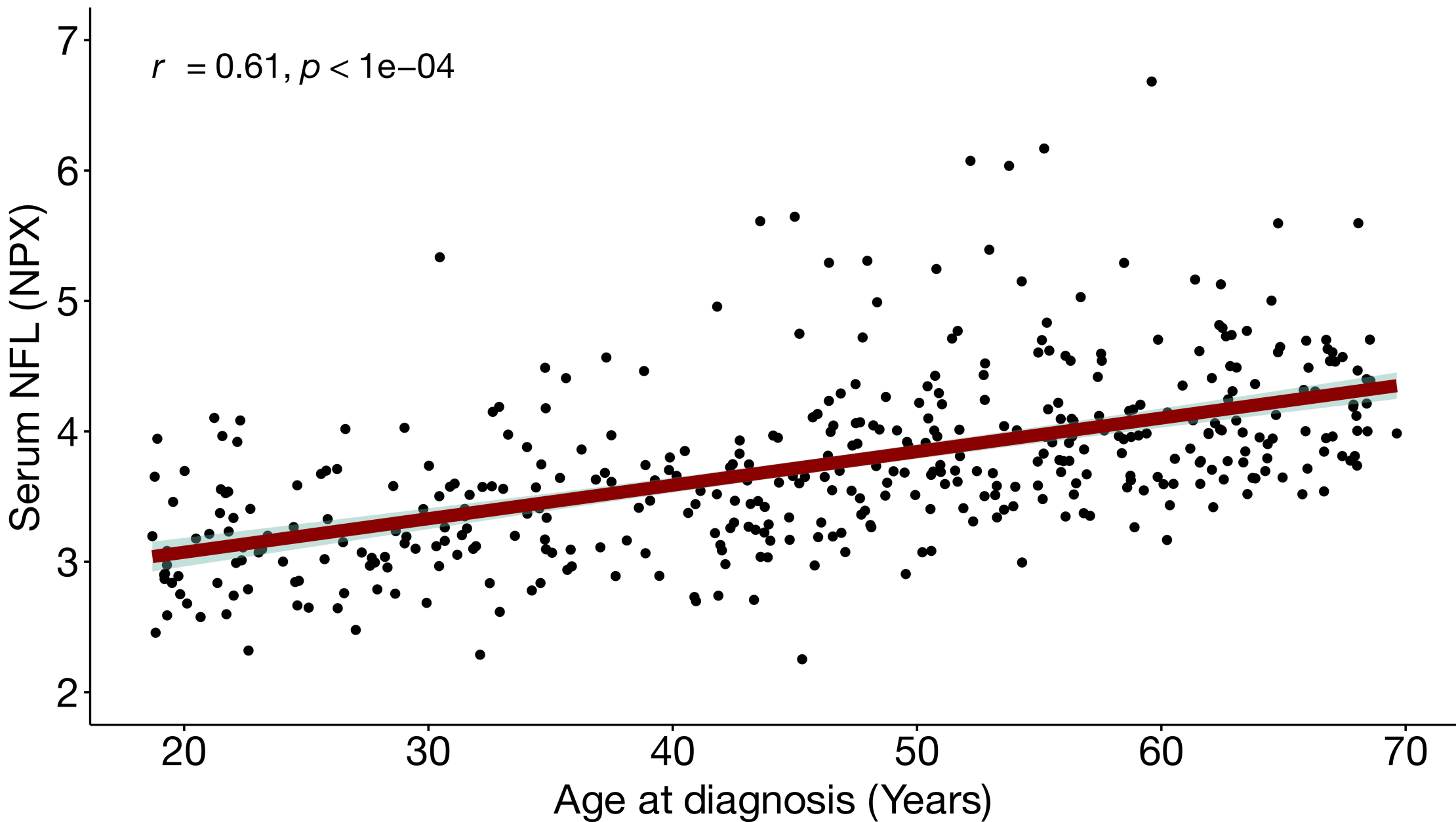


ESM Fig.3. Serum NFL levels by DSPN stages

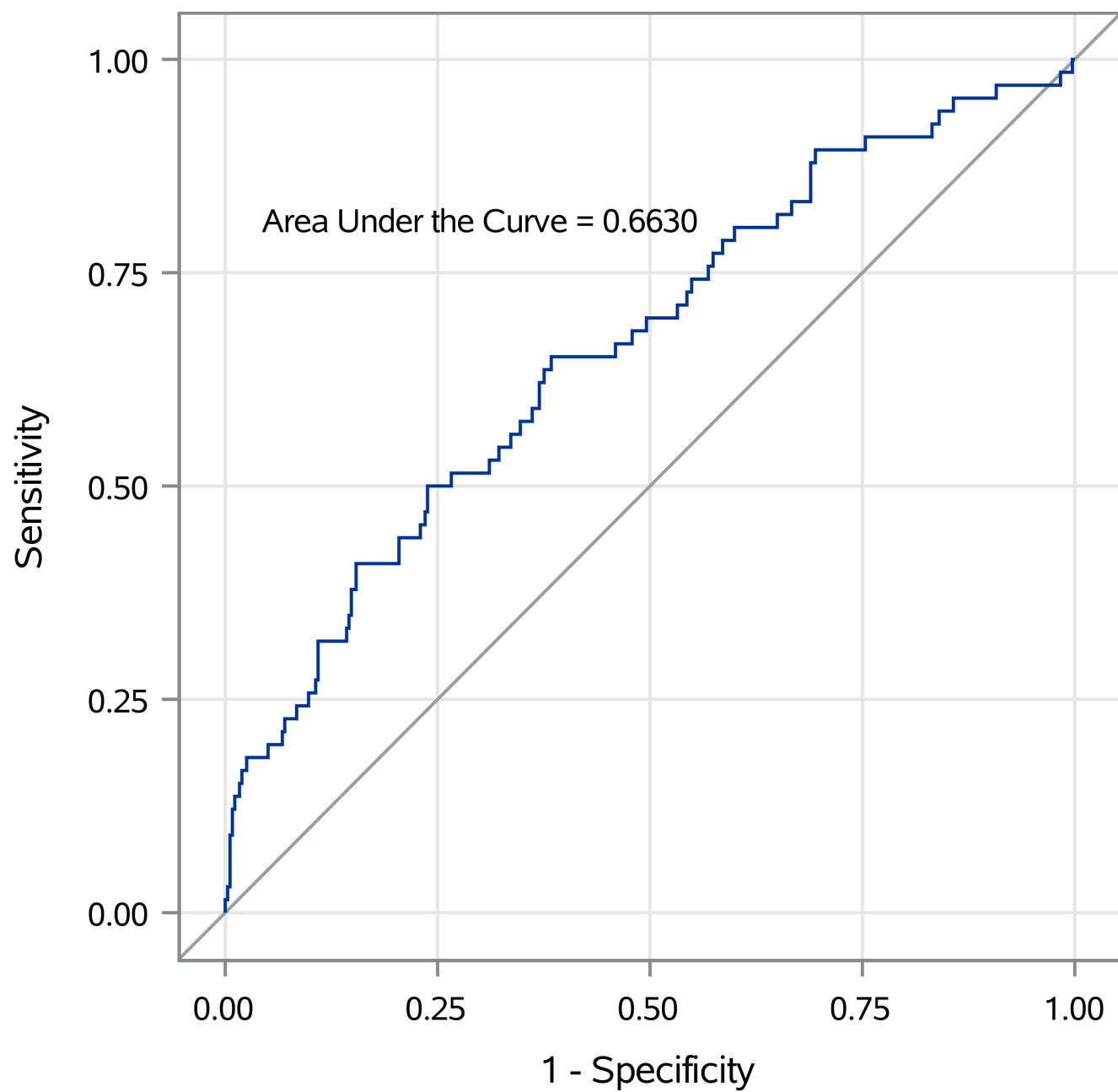


0= No DSPN, 1= Subclinical DSPN, 2= Confirmed asymptomatic DSPN, 3= Confirmed symptomatic DSPN
The boxplots with jittered data points show the distribution of serum NFL according to DSPN stage.
The line that divides the box into 2 parts represents the median of the data.
The ends of the box show the upper (Q3) and lower (Q1) quartiles.
The extreme line shows $Q3+1.5 \times IQR$ to $Q1-1.5 \times IQR$

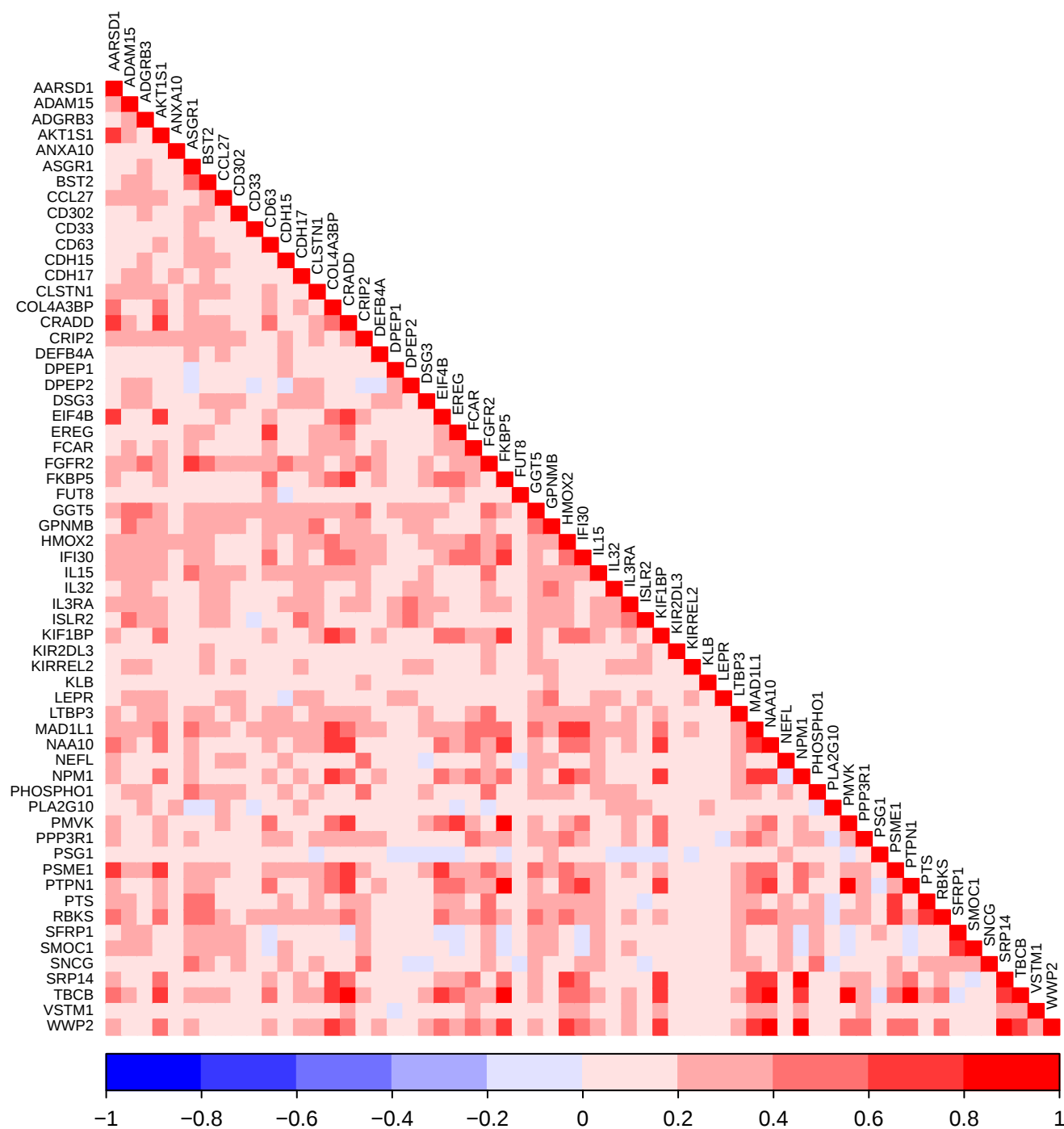
ESM Fig.4. Spearman correlation of serum NFL and age at diagnosis



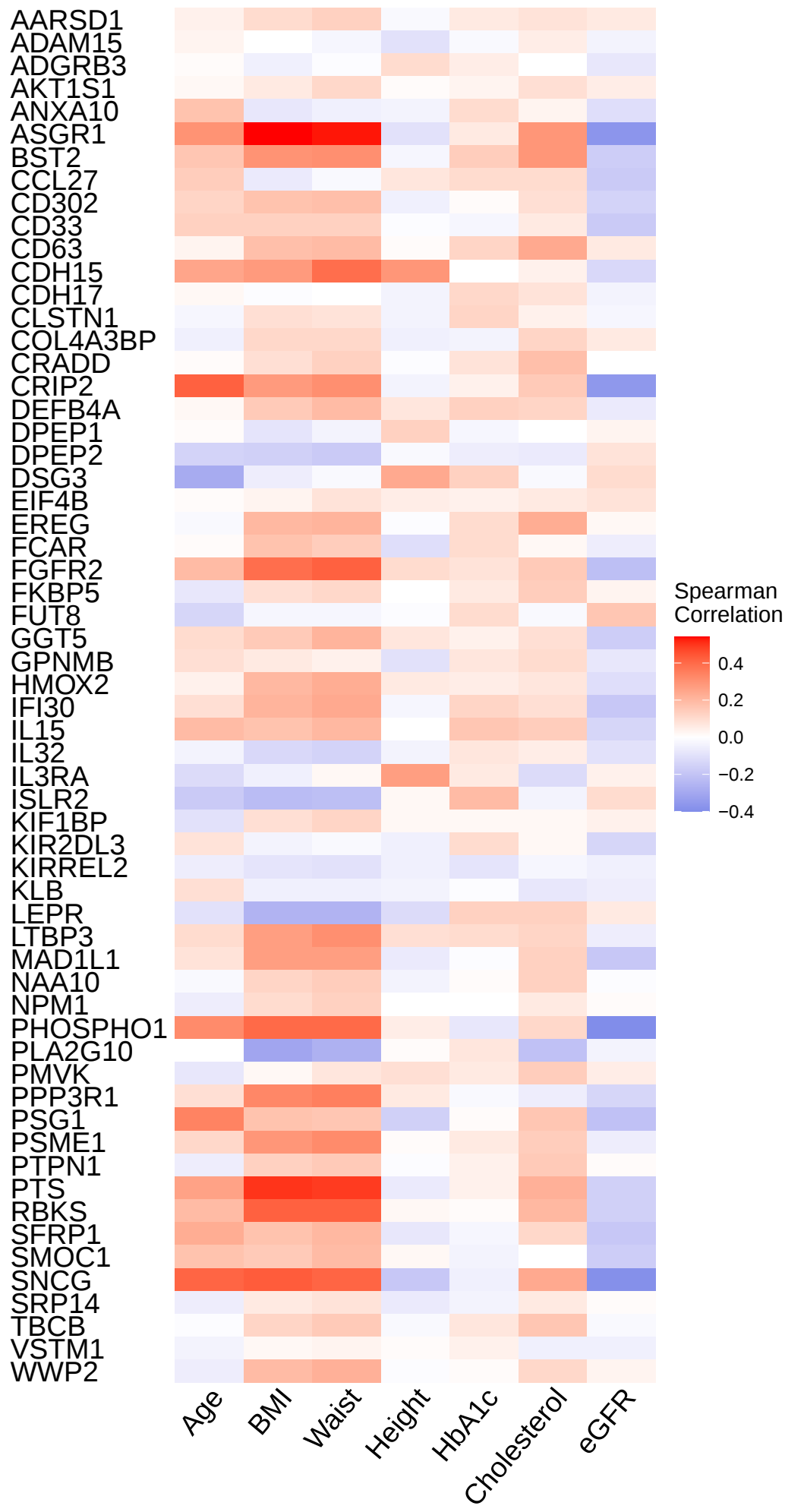
ESM Fig.5. ROC curve of serum NFL



ESM Fig.6. Spearman correlations among all neurological biomarkers

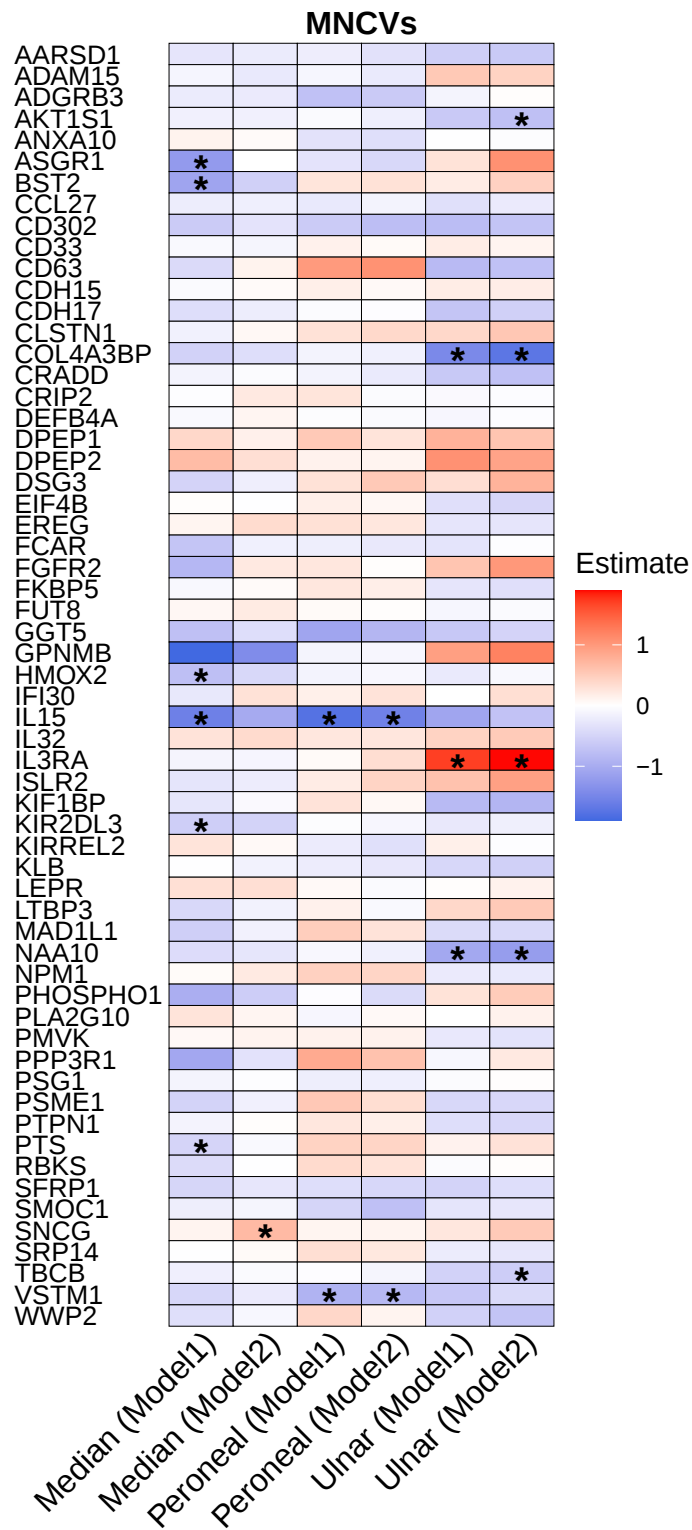


ESM Fig.7. Correlations of biomarkers with covariates

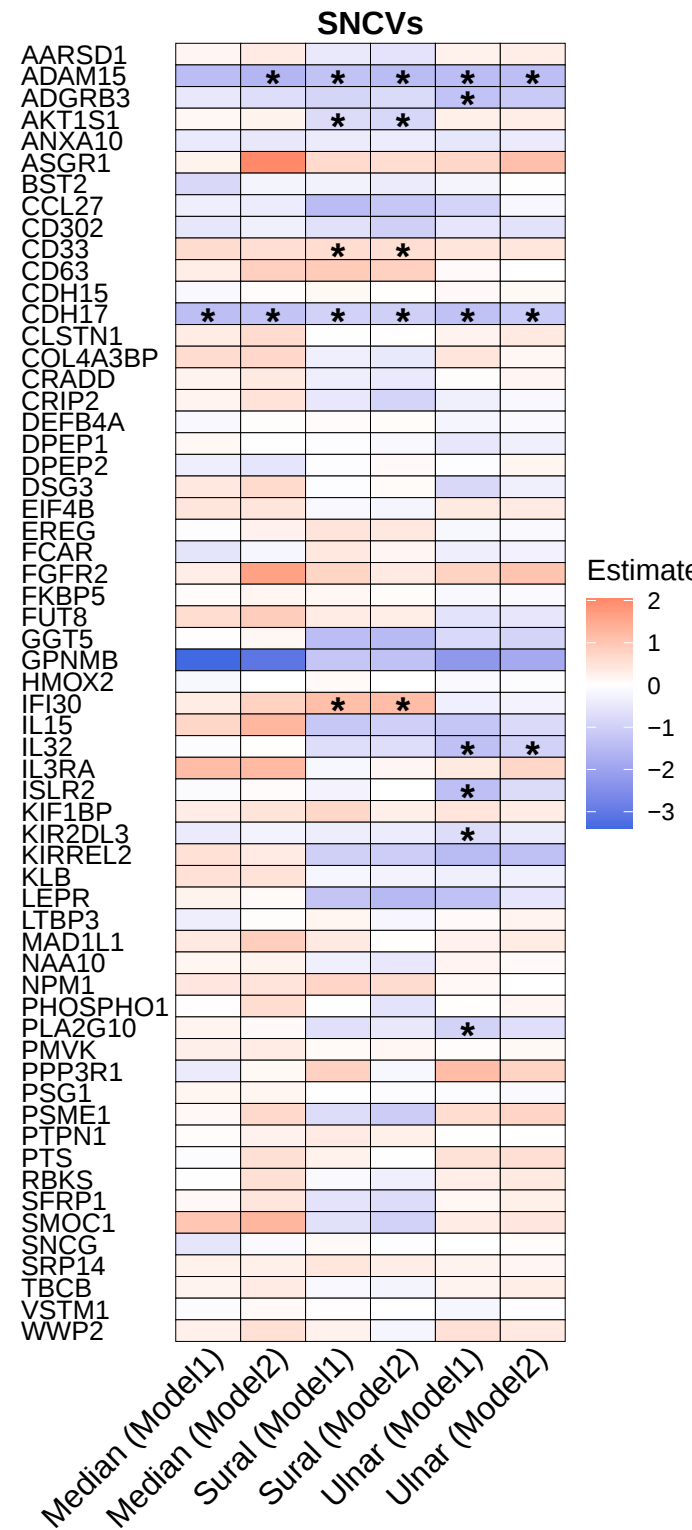


ESM Fig.8. Beta estimates for the associations of biomarkers (per 1-NPX increase) with nerve conduction velocities

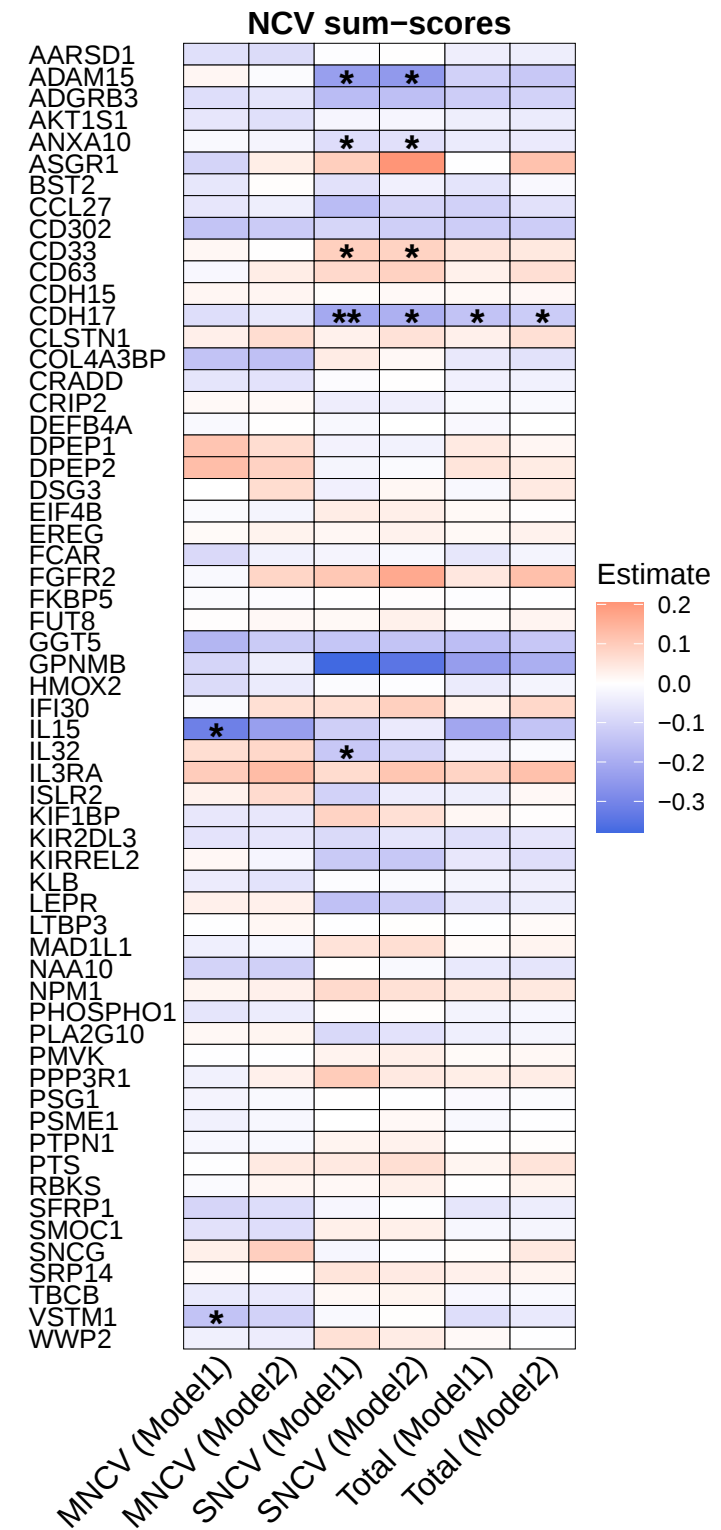
A



B



C



*p <0.05; **Bonferroni-corrected p<0.0008 indicates statistical significance, MNCV; motor nerve conduction velocity, SNCV; sensory nerve conduction velocity

