frontiers

The Metallome as a link between the 'Omes' in Autism Spectrum Disorders

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Supplementary Table 1: On overview of "Omics" studies in ASD (Metallomics, Proteomics, Transcriptomics, Epigenomics, Metabolomics, Microbiomics, Inflammasomics)

Reference	Species	Method of analysis	Finding
Metallomics			
1	Human	Meta-analysis	↑Cu ↓Zn, Fe
2	Human	Meta-analysis	↑Pb, Hg
3	Human	Mass spectrometry	↑Cd ↓Zn, Cu, Mn, Cu
4	Human	ICP-Mass spectrometry	↑Al, Pb, Hg ↓Zn, Mg
5	Human	ICP-Mass spectrometry	↑Pb ↓Mn, Zn
6	Human	Inductively coupled plasma optical emission spectrometer	↑Pb, Hg, Cd ↓Zn, Mn
7	Human	Atomic absorption spectrometry	↑Cu, Pb, Hg ↓Zn, Mg
8	Human	ICP-Mass spectrometry	↑ ↓Ni, Cr,Al, Mn
9	Human	Atomic absorption spectrometry	↑Pb ↓Mn
10	Human	Meta-analysis	↓Ferritin , No significant difference in serum Fe
11	Human	Meta-analysis	↓Zn
12	Human	Meta-analysis	↓Zn/Cu
13	Human	ICP-Mass spectrometry	↑Cu ↓Zn
14	Human	Roentgen-fluorescence spectrometry	↑Cu, Pb, Hg, Cd ↓Zn, Mn
15	Human	Mass-spectrometry	↑Cu ↓Zn, Zn/Cu
16	Human	ICP-Atomic emission spectrometry	↑Zn, Fe, Ni, Cd, As
17	Human	Mass spectrometry	↑Zn, Fe, Mg ↓Cu
18	Human	Atomic absorption spectrometry	↑Cu, Pb, Hg ↓Zn, Al
19	Human	ICP-Mass spectrometry	↑Hg
20	Human	ICP-Mass spectrometry	↓Zn
21	Human	ICP-Mass spectrometry	↓Zn, Cu, Mg, Cr, Mn
22	Human	Atomic absorption spectrometry	↑Pb, Cu ↓Hg, Zn
23	Human	Atomic absorption spectrometry	↑Cu, Pb, Hg ↓Zn, Mg
24	Human	Spectrophotometry	↑Hg
25	Human	ICP-Mass spectrometry	↑Pb
26	Human	High-pressure liquid chromatography with fluorometric detection	↑Hg
27	Human	HPLC spectrofluorometry	↑Toxic metal markers (Porphyrin)
28	Human	Atomic absorption spectrometry	↑Hg, Pb, Cd ↓Cu, Mn, Fe
29	Human	Mass spectrometry	↑Hg, Pb
30	Human	Systemic analysis	↑Pb

31	Human	Case report, treatment for elevated Pb levels with chelating agent succimer	↓Pb levels during treatment
Proteomics/Transcriptomics			
32	Human	Blood biomarker analysis	↑IgD, suPAR, MAPK14, EPHB2, and DERM
33	Mouse	Illuminaseq.	↑ERK, RPLP1, RPL36A, DRD1
34	Mouse	Illumina seq.	↓mTORC1
35	Human	Metatranscriptomic analysis	↓parvalbumin, ↑TNF, HDAC1, GATA2
36	Human	LC-MS	↑Tubulin, MAPT, DLG4, APP, PSEN1, HDAC4, HTT
37	Mouse	Protein interaction/ Immunofluorescence	↑TLR4, Phospho-NFκB p65, IKKα, and IBA-1, iNOS ↓Arg-1
38	Human	Microarray analysis	↑IKKα ↓Tyk2, EIF4G1, PRKCI
39	Human	Protein expression	↑Alpha-2-macroglobulin, Alpha-1-antitrypsin, Haptoglobin, Fibrinogen, Transferrin, Prealbumin, Apolipoprotein A-I Apolipoprotein A-IV, Apolipoprotein J, Albumin
40	Human	Redox proteomics	↑C8 alpha chain, Ig kappa chain C
41	Human	LC-ESI-MS	↓Apo B-100 ↑Complement C1q subcomponent- C chain, Fibronectin 1, Complement factor H
42	Human	RP-HPLC-ESI-MS	↓Statherin, Histatin-1, Aprp, PRP-1, PRP-3
43	Human	MALDI-ToF-MS	↑Low molecular weight proteins such as serotonin, norepinephrin and neurotrophic factors
44	Human	Mass spectrometry	↑C3 complement protein
45	Human	Nano liquid chromatography-tandem mass spectrometry	↑PIP, LTF, annexin A1, neutrophil-defensin-1, lactoperoxidase, lipocalin-1 ↓salivary acidic proline-rich phospho-protein 1/2, submaxillary gland androgen-regulated protein 3B, antileukoproteinase, pleckstrin-homology domain-containing fam-ily H member, statherin
46	Human	NanoLC-MS/M	↑FRAT1, Kinesin family member 14, Integrin alpha6 subunit, growth hormone regulated TBC protein 1, parotid secretory protein, Prolactin-inducible protein precursor, Mucin-16, MRP14 ↓Alpha-amylase, CREB-binding protein, p532, Transferrin, Zn alpha2 glycoprotein, Zymogen granule protein 16, cystatin D, plasminogen
47	Human	MALDI–TOF–MS	↑Excretion of KNG-1, IgG1 heavy chain variable region, mannan-binding lectin serine protease-2 isoform-2 precursor
48	Human	NanoLC-MS/M	↑APOE, Serpina 1, FLBN1, FN1, C3, C5, AGT, VTN, Serpina 4, IGFALS ↓ACTN1, CALM1, CALR, ACTG1, PARVb, MAPRE2, ENO1, ITGA2B, FERMT3, EHD3, TLN1, VCL, VCP, THBS1
49	Human	MALDI-TOF MS	↑Serpina 5, platelet factor 4 (PF4), fatty acid binding protein 1(FABP1), apolipoprotein C-I precursor (APOC1), alpha-fetoprotein precursor (AFP), carboxypeptidase B2 (CPB2), trace amine-associated receptor 6 (TAAR6), and isoform1 of fibrinogen alpha chain precursor (FGA)
50	Human	SRM-MS	↑GFAP, CKB, SYN2, STBP1 ↓VIME, MAG, PLP1, STX1, SYT1, PACSIN1
51	Mouse	Microarray analysis	↑Stxbp1, Tom1l2, Agk, Gap43 ↓Rock2, Arl1,

52	Mouse	LC-MS/MS	↑MAP2, FKBP15, Snapin, TRF, MAP2 ↓MBP, UBE3A, MAP6, STXBP1
53	Rat	LC-MS/MS	MAPK, SUMO3, SNCA, PARK7 are candidate common hubs in Tuber-sclerosis complex
54	Mouse	SILAC	↑APC, FUS, tPA, SERBP, N-CAM↓Kcnma1α, VILIP, ARVCF
55	Mouse	LC-MS/MS	↑Auts2, Foxp1, core histone macro-H2A.2, Purα ↓Shank1-3, clusterin, alpha-1-antitrypsin 1, apolipoprotein A-I, HSPH1, HSP90α, HSP90β, HSPA4
56	Human	HPLC-MS/MS	↑Alterations present in Fibrinogen, Actin, Vinculin, Gelsolin
57	Mouse	LC–MS/MS	↑PSD95 ↓Synaptophysin, GluA1, GluA2, GluN1, GluN2B, GluK5
58	Mouse	LC-MS	Altered interactions of DLG, DLGAP and SHANK in postsynaptic density throughout development
59	Mouse	Agilent-014868 Whole Mouse Genome Microarray	En2-/- cerebellum: ↑immune response and major histocompatibility complex-related immunity. En2-/- hippocampus: ↓neurotransmission ↑seizures
60	Mouse	Affymetrix Mouse Genome 430 2.0 Array	Pten and Mecp2 knockdown lead to the most alterations in gene expression
61	Mouse	Affymetrix Mouse Gene 1.0 ST Array	CNV's in 16p11.2 result in dosage dependent alterations in 26 genes such as in *Gdpd3*
62	Mouse	Agilent-014868 Whole Mouse Genome Microarray	BTBR: ↑Microglial genes. En2−/− : ↑glutamatergic postsynaptic genes, FMRP-interacting genes and epilepsy-related genes
63	Mouse	Affymetrix Mouse Gene 1.1 ST Array	Altered expression of 116 in the nucleus accumbens and 251 genes in the medial prefrontal cortex. Many played roles in myelin functionality and stability.
64	Human	Published transcriptomic dataset analysis	For the ASD Convergent subtype, 13 distinct associated mRNA co-expression modules were identified along with 43 alternatively expressed miRNAs, 28 upregulated and 15 downregulated.
65	Mouse	Illumina HiSeq. Gene expression levels were quantified using featureCounts	Convergence on primarily neuronal (Nefh, Elavl4, Dclk, Cend1, Ina, and Chga) and mitochondrial (Atp5b, Slc25a3, Bcat1, Idh3a) genes was detected in three mouse models and compared to post-mortem human samples.
66	Human	Freeze 1 and 2 of the PsychENCODE Consortium dataset	Identification of neuronal and synaptic signaling genes and glial-immune or neuroinflammatory signals involving IFN-response, NFkB, astrocytes, and microglia as key alterations.
67	Human	Published transcriptomic dataset analysis	Genes related to mitochondrial function were differentially expressed in autism cerebral cortex and correlated with genes related to synaptic transmission.
68	Human	Illumina Ref8 v3 microarrays	444 genes with significant expression changes in ASD cortex and 2 genes in cerebellum implicating synaptic dysfunction, microglial, and immune dysregulation
Epigenomics			
69	Human	ChIP sequencing, RNA sequencing	↑Gene modules (MG4, MG5, MG51)
70	Human	Illumina & EWAS	455,068 CpG sites associated with ASD, 48 had suggestive significance
71	Human	ChIP sequencing, Fluorescence sorting	↑Histone H3 lysine 4 methylation and Histone H3 lysine 27 acetylation
72	Mouse	rt-PCR	Methylation of CpG sites↑Mid1,Nlgn1, Nf2, Nrgn1, Nrxn2, Neurod6, Efnb3, ↓Wnt3, Dlx1, Nlgn1, Nf2

73	Mouse	qrt-PCR	↑Methylation of promoter region in GAD1, GAD2 due to prenatal immune activation
74	Human	rt-PCR	↓Methylation of miR-142 promoter region
75	Human	Immunoprecipitation assays	↑Methylation of GAD1 promoter, no change observed in GAD2 and RELN promoters
76	Human	ChIP-sequencing	↑Acetylation of SLC30A5, CACNA1C, GRIN2B ↓HDA2, HDAC4, CX3CR1, FGFR2, CX3CR1, GRB10
64	Human	Meta-data analysis	A differential acetylation analysis found 2156 differentially acetylated regions at an FDR < 20%, identification of 3013 differentially methylated gene promoters, 2298 hypermethylated and 715 hypomethylated in ASD
77	Rat	RNA sequencing	17/37 MeCP-binding proteins are splicing factors, MeCP2 interacts with 5hmC and through epigenetic changes in histone markers can regulate mRNA splicing
Metabolomics			
78	Rat	NMR spectroscopy	Hippocampal conc. ↑NAA, Glu, and Gln, pyroglutamate, uracil, UFA, isoleucine, serine, tyrosine, phenylalanine, Lac, Asp, NA Cerebral conc. ↓phenylalanine, valine, alanine, glycine, isoleucine, glycerol
79	Human	Mass-spectrometry	Not gender specific
80	Human	NMR spectroscopy	↑Fumarate, Cis-aconitate, Carnitine, Glutamate (correlated with better social skills)
81	Human	Mass-spectrometry	↓7-Methylxanthine, Scylloinositol, Uric acid, Aminomalonic acid ↑Quinic acid, Hippuric acid, Tryptophan, 1-Methylhistidine, Cystine, Indole-3-acetic acid, Allylthioacetic acid, Leucine, Lactic acid
82	Human	Mass-spectrometry	Positive correlation identified between the level of Clostridium species and methyl esters (butanoic acid methyl ester, acetic acid methyl ester and pentanoic acid methyl ester) and indoles. Faecalibacterium, Ruminococcus and Bifidobacterium genera are positively correlated to the total SCFA. Bacteroides genus are correlated with total Free amino acids and propionic acid
83	Human	Flow-cytometric assay	↑COX-2, mPGES-1, PGE2
Microbiomics			
84	Human	Illumina seq.	↑ Acidobacteria,↓Firmicutes
85	Human	Pyrosequencing	↓Acidobacteria,↑Bacteroidetes, ↓Cyanobacteria, ↓Firmicutes, ↑Proteobacteria, ↑Tenericutes
86	Human	16S sequencing	↓Acidobacteria, ↑Bacteroidetes, ↑Proteobacteria
87	Mouse	Illumina seq.	↑ Acidobacteria, ↑Bacteroidetes
88	Mouse	Pyrosequencing	↑ Acidobacteria,↑Deferribacteres, ↑Firmicutes, ↑Tenericutes, ↓ Verrucomicrobia
89	Mouse	16S sequencing	↓Acidobacteria, ↑Bacteroidetes, ↓Firmicutes
90	Human	In silico analysis	↑Bacteroidetes
91	Human	Pyrosequencing	↓Bacteroidetes
92	Human	Pyrosequencing	↓Bacteroidetes
93	Human	Illumina seq.	↓Bacteroidetes, ↓Firmicutes
94	Mouse	Pyrosequencing	↓Bacteroidetes,↓Deferribacteres, ↑Firmicutes
95	Mouse	Illumina seq.	↑Bacteroidetes, ↓Cyanobacteria, ↓Firmicutes, ↑ Verrucomicrobia
96	Human	16S sequencing	↓Firmicutes

97	Mouse	16S sequencing	↑Proteobacteria
Inflammasomics			
98	Human	Meta-analysis	↓IL-10, IL-1 receptor antagonist. ↑IL-5. IFNα, IL-13
99	Human	Flow-cytometric assay	↓IFN-γ, IL-4, IL-10
100	Human	Luminex xMAP technology	↑IL-4, IL-10, TNFα, TNFβ
101	Human	qRT-PCR	↑IL-6
82	Human	Flow-cytometric assay	↑NFkB
102	Human	ELISA assay	↑IL-6, TNF
103	Human	Luminex cytokine assay	↑IL-6, IL-12
104	Human	RT-PCR array	↑AIM2 & NLRP3 inflammasomes, IL-1β, IL-18

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