

Twin Research and Human Genetics

Title: ErbB signaling pathway genes are differentially expressed in monozygotic twins discordant for sports-related concussion

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Supplementary Table S1. Analytical approach for determining important longitudinal changes in gene expression

	Longitudinal Δ in mRNA expression		
	Baseline Pre-Injury (T_0) to Acute Post-Injury (T_1)	Baseline Pre-Injury (T_0) to Subacute Post-Injury (T_2)	Acute Post-Injury (T_1) to Subacute Post-Injury (T_2)
Twin A (Concussed)	$T_1 - T_0 = \Delta A_{(T1-0)}$	$T_2 - T_0 = \Delta A_{(T2-0)}$	$T_2 - T_1 = \Delta A_{(T2-1)}$
Twin B (Control)	$T_1 - T_0 = \Delta B_{(T1-0)}$	$T_2 - T_0 = \Delta B_{(T2-0)}$	$T_2 - T_1 = \Delta B_{(T2-1)}$
Difference between twins in longitudinal Δ of mRNA expression	$\Delta A_{(T1-0)} - \Delta B_{(T1-0)}$	$\Delta A_{(T2-0)} - \Delta B_{(T2-0)}$	$\Delta A_{(T2-1)} - \Delta B_{(T2-1)}$

Supplementary Table S2a. Genes with up-regulated mRNA expression from baseline to acute post-concussion time points in MZ twins

Gene Name	Gene Symbol	Difference between twins in longitudinal Δ in mRNA expression
fibrillin 2	FBN2	2.06
Ras and Rab interactor 2	RIN2	2.04
IKAROS family zinc finger 1 (Ikaros)	IKZF1	2.01
lymphoid-restricted membrane protein	LRMP	1.99
family with sequence similarity 3, member C	FAM3C	1.88
capping protein (actin filament) muscle Z-line, alpha 2	CAPZA2	1.87
siah E3 ubiquitin protein ligase 1	SIAH1	1.81
long intergenic non-protein coding RNA 597	LINC00597	1.79
G protein-coupled receptor 155	GPR155	1.79
proteasome maturation protein	POMP	1.79
RAB11 family interacting protein 3 (class II)	RAB11FIP3	1.78
family with sequence similarity 129, member C	FAM129C	1.77
formin binding protein 4	FNBP4	1.74
ribosomal protein S24	RPS24	1.72
nuclear receptor subfamily 1, group H, member 4	NR1H4	1.71
spindlin family, member 3	SPIN3	1.70
ubiquitin protein ligase E3 component n-recognin 2	UBR2	1.70
polymerase (RNA) II (DNA directed) polypeptide B, 140kDa	POLR2B	1.67
neurofibromin 2 (merlin)	NF2	1.66
thyroid adenoma associated	THADA	1.65
long intergenic non-protein coding RNA 1560	LINC01560	1.65
oxysterol binding protein	OSBP	1.65
chemokine (C-C motif) receptor 6	CCR6	1.64
zinc finger protein 785	ZNF785	1.63
FYVE, RhoGEF and PH domain containing 4	FGD4	1.62
leucine rich repeat (in FLII) interacting protein 1	LRRFIP1	1.61
density-regulated protein	DENR	1.60
YTH domain containing 1	YTHDC1	1.60
nebulin	NEBL	1.58
nuclear factor, erythroid 2-like 3	NFE2L3	1.57
cysteine and glycine-rich protein 2	CSRP2	1.56
U2 snRNP-associated SURP domain containing	U2SURP ^a	1.55
G protein-coupled receptor 157	GPR157	1.54
fibronectin type III and SPRY domain containing 1-like	FSD1L	1.54
DNA replication helicase/nuclease 2	DNA2	1.53
membrane-spanning 4-domains, subfamily A, member 3 (hematopoietic cell-specific)	MS4A3	1.53
olfactory receptor, family 7, subfamily D, member 2	OR7D2	1.52
HOXA transcript antisense RNA, myeloid-specific 1	HOTAIRM1	1.50

^a Probe ID: 236431_at

Supplementary Table S2b. Genes with down-regulated mRNA expression from baseline to acute post-concussion time points in MZ twins

Gene Name	Gene Symbol	Difference between twins in longitudinal Δ in mRNA expression
prolyl 3-hydroxylase 2	P3H2	-2.25
immunoglobulin lambda constant 1 (Mcg marker)	IGLC1	-2.00
pregnancy specific beta-1-glycoprotein 6	PSG6	-2.00
immunoglobulin kappa constant	IGKC ^b	-1.99
immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	IGJ	-1.95
calcium channel, voltage-dependent, L type, alpha 1F subunit	CACNA1F	-1.90
tumor necrosis factor receptor superfamily, member 17	TNFRSF17	-1.90
solute carrier family 25, member 48	SLC25A48	-1.83
caspase 2, apoptosis-related cysteine peptidase	CASP2	-1.81
carboxypeptidase D	CPD	-1.78
cyclin-dependent kinase 1	CDK1	-1.78
spermatogenesis and oogenesis specific basic helix-loop-helix 2	SOHLH2	-1.77
ectonucleotide pyrophosphatase/phosphodiesterase 7	ENPP7	-1.76
transmembrane protein with EGF-like and two follistatin-like domains 2	TMEFF2	-1.75
epidermal growth factor receptor	EGFR ^c	-1.69
MAPT antisense RNA 1	MAPT-AS1	-1.69
NK3 homeobox 1	NKX3-1	-1.67
t-complex-associated-testis-expressed 3	TCTE3	-1.66
disrupted in renal carcinoma 2	DIRC2	-1.65
lipase, member H	LIPH	-1.63
long intergenic non-protein coding RNA 877	LINC00877	-1.63
long intergenic non-protein coding RNA 1144	LINC01144	-1.63
early growth response 1	EGR1	-1.62
splicing factor, suppressor of white-apricot family	SFSWAP	-1.62
C1q and tumor necrosis factor related protein 1	C1QTNF1	-1.62
basonuclin 2	BNC2	-1.61
CD6 molecule	CD6	-1.60
fibroblast growth factor receptor 2	FGFR2	-1.60
protein kinase, cGMP-dependent, type II	PRKG2	-1.57
mitochondrial ribosomal protein L47	MRPL47	-1.57
epidermal growth factor receptor	EGFR ^d	-1.57
ATPase, Ca ⁺⁺ transporting, cardiac muscle, slow twitch 2	ATP2A2	-1.56
septin 4	SEPT4	-1.55
ubiquitously transcribed tetratricopeptide repeat containing, Y-linked	UTY	-1.54
epoxide hydrolase 4	EPHX4	-1.54
heat shock protein, alpha-crystallin-related, B6	HSPB6	-1.54
calpastatin	CAST	-1.54
protein tyrosine phosphatase, non-receptor type 1	PTPN1	-1.53
endogenous retrovirus group H, member 6	ERVH-6	-1.52
adaptor-related protein complex 1, sigma 3 subunit	AP1S3	-1.51
immunoglobulin kappa constant	IGKC ^e	-1.51

^b Probe ID: 214768_x_at, ^c Probe ID: 1565484_x_at, ^d Probe ID: 1565483_, ^e Probe ID: 214669_x_at

Supplementary Table S3a. Genes with up-regulated mRNA expression from baseline to sub-acute post-concussion time points in MZ twins

Gene Name	Gene Symbol	Difference between twins in longitudinal Δ in mRNA expression
mitochondrial ribosomal protein L19	MRPL19	2.13
G protein-coupled receptor 155	GPR155	2.12
polymerase (RNA) II (DNA directed) polypeptide B, 140kDa	POLR2B	1.95
family with sequence similarity 3, member C	FAM3C	1.87
RUN and FYVE domain containing 2	RUFY2	1.87
Rho-related BTB domain containing 3	RHOBTB3	1.85
Kruppel-like factor 12	KLF12	1.85
transcription factor 7-like 2 (T-cell specific, HMG-box)	TCF7L2	1.84
ELK4, ETS-domain protein (SRF accessory protein 1)	ELK4	1.81
long intergenic non-protein coding RNA 597	LINC00597	1.81
protein tyrosine phosphatase, non-receptor type 4 (megakaryocyte)	PTPN4	1.80
nicotinamide nucleotide adenyltransferase 3	NMNAT3	1.77
glutamate-cysteine ligase, modifier subunit	GCLM	1.75
epiregulin	EREG	1.73
long intergenic non-protein coding RNA 1578	LINC01578	1.72
Ras and Rab interactor 2	RIN2	1.72
protein tyrosine phosphatase, receptor type, C	PTPRC ^f	1.71
PEST proteolytic signal containing nuclear protein	PCNP	1.71
NEDD4 binding protein 2-like 2	N4BP2L2	1.70
killer cell lectin-like receptor subfamily C, member 4	KLRC4	1.68
ectonucleotide pyrophosphatase/phosphodiesterase 5 (putative)	ENPP5 ^g	1.68
proteasome (prosome, macropain) subunit, beta type, 7	PSMB7	1.68
exportin 7	XPO7	1.67
transmembrane protein 229B	TMEM229B	1.66
ataxin 1	ATXN1	1.65
ARP2 actin-related protein 2 homolog (yeast)	ACTR2	1.64
U2 snRNP-associated SURP domain containing	U2SURP ^h	1.64
TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 68kDa	TAF15	1.62
pyrophosphatase (inorganic) 2	PPA2	1.61
platelet factor 4 variant 1	PF4V1	1.60
metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)	MALAT1	1.59
protein tyrosine phosphatase, receptor type, C	PTPRC ⁱ	1.58
lysozyme G-like 2	LYG2	1.57
tumor necrosis factor receptor superfamily, member 25	TNFRSF25	1.57
DDB1 and CUL4 associated factor 17	DCAF17	1.57
leucine rich repeat (in FLII) interacting protein 1	LRRFIP1	1.56
phospholipase D1, phosphatidylcholine-specific	PLD1	1.56
ectonucleotide pyrophosphatase/phosphodiesterase 5 (putative)	ENPP5 ^j	1.56
neuregulin 1	NRG1	1.54
cytoplasmic polyadenylation element binding protein 4	CPEB4	1.54
MCM3AP antisense RNA 1	MCM3AP-AS1	1.54

family with sequence similarity 129, member C	FAM129C	1.54
synaptotagmin-like 3	SYTL3	1.53
pyrin and HIN domain family, member 1	PYHIN1	1.53
sperm associated antigen 1	SPAG1	1.52
zinc finger protein 578	ZNF578	1.52
mechanistic target of rapamycin (serine/threonine kinase)	MTOR	1.51
Rho-related BTB domain containing 3	RHOBTB3	1.51
CD24 molecule	CD24	1.51
adhesion G protein-coupled receptor G1	ADGRG1	1.50

^fProbe ID: 1569830_at, ^gProbe ID: 237054_at, ^hProbe ID: 236696_at, ⁱProbe ID: 1552480_s_at, ^jProbe ID: 227803_at

Supplementary Table S3b. Genes with down-regulated mRNA expression from baseline to sub-acute post-concussion time points in MZ twins

Gene Name	Gene Symbol	Difference between twins in longitudinal Δ in mRNA expression
transmembrane protein with EGF-like and two follistatin-like domains 2	TMEFF2	-2.80
epidermal growth factor receptor	EGFR ^k	-2.41
immunoglobulin kappa constant	IGKC	-2.19
prolyl 3-hydroxylase 2	P3H2	-2.01
epidermal growth factor receptor	EGFR ^l	-1.91
BicC family RNA binding protein 1	BICC1	-1.86
ribosomal protein S11	RPS11	-1.85
S100 calcium binding protein A8	S100A8	-1.84
spermatogenesis and oogenesis specific basic helix-loop-helix 2	SOHLH2	-1.81
RAB30, member RAS oncogene family	RAB30	-1.69
caspase 2, apoptosis-related cysteine peptidase	CASP2	-1.63
sialophorin	SPN	-1.59
pleckstrin homology-like domain, family B, member 3	PHLDB3	-1.59
long intergenic non-protein coding RNA 1016	LINC01016	-1.57
mitotic spindle organizing protein 1	MZT1	-1.55
glycine dehydrogenase (decarboxylating)	GLDC	-1.55
Rh-associated glycoprotein	RHAG	-1.54
tumor necrosis factor receptor superfamily, member 17	TNFRSF17	-1.54
solute carrier family 22 (organic anion/urate transporter), member 12	SLC22A12	-1.54
enolase 1, (alpha)	ENO1	-1.52
ADP-ribosyltransferase 4 (Dombrock blood group)	ART4	-1.51

^k Probe ID: 1565483_at , ^lProbe ID: 1565484_x_at

Supplementary Table S4a. Genes with up-regulated mRNA expression from acute to sub-acute post-concussion time points in MZ twins

Gene Name	Gene Symbol	Difference between twins in longitudinal Δ in mRNA expression
glutamine and serine rich 1	QSER1	2.19
poly(rC) binding protein 2	PCBP2	1.92
epiregulin	EREG	1.67
zinc finger protein 541	ZNF541	1.66
exportin 7	XPO7	1.65
DENN/MADD domain containing 1B	DENND1B	1.64
general transcription factor IIH, polypeptide 5	GTF2H5	1.62
lysine (K)-specific methyltransferase 2C	KMT2C	1.60
synaptic vesicle glycoprotein 2B	SV2B	1.57
LIM domain binding 2	LDB2	1.57
ADAM metalloproteinase with thrombospondin type 1 motif, 1	ADAMTS1	1.56
DNA replication and sister chromatid cohesion 1	DSCC1	1.55
protein tyrosine phosphatase, receptor type, C	PTPRC ^m	1.55
ataxin 3	ATXN3	1.54
protease, serine, 23	PRSS23	1.53
InaD-like (Drosophila)	INADL	1.53
glutamate receptor, ionotropic, N-methyl D-aspartate 2D	GRIN2D	1.52
aldo-keto reductase family 1, member C3	AKR1C3	1.52
killer cell lectin-like receptor subfamily B, member 1	KLRB1	1.52
myosin, heavy chain 10, non-muscle	MYH10	1.52
IKAROS family zinc finger 3 (Aiolos)	IKZF3	1.51
PIF1 5'-to-3' DNA helicase	PIF1	1.50
ataxin 1	ATXN1	1.50

^m Probe ID: 1552480_s_at

Supplementary Table S4b. Genes with down-regulated mRNA expression from acute to sub-acute post-concussion time points in MZ twins

Gene Name	Gene Symbol	Difference between twins in longitudinal Δ in mRNA expression
mitotic spindle organizing protein 1	MZT1	-1.76
pleckstrin homology-like domain, family B, member 3	PHLDB3	-1.55
mediator complex subunit 18	MED18	-1.53
peptidyl arginine deiminase, type IV	PADI4	-1.53
dachshund family transcription factor 1	DACH1	-1.51
ceroid-lipofuscinosis, neuronal 8 (epilepsy, progressive with mental retardation)	CLN8	-1.50