

Spinal Muscular Atrophy Foundation

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# Introduction

### Background:

Biomarkers are measures of biological state that are useful in assessing disease severity, designing proof of concept trials, tracking therapeutic responses, and generating hypotheses about disease pathophysiology. Biomarkers in Spinal Muscular Atrophy (SMA) related to muscle and nerve physiology, imaging, SMN protein and transcript are being explored in other initiatives, and there is also a need to investigate potential new plasma protein biomarkers that could aid in prognosis or monitoring treatment efficacy in SMA patients.

### **Objective:**

Our objective was to use a multiplexed immunoassay panel (MAP) technology to expand on the plasma protein biomarker discovery aspect of the prospective Biomarkers for SMA (BforSMA) clinical study conducted in 2009 and create a custom biomarker panel for SMA for use in the research and clinical communities.

### Strategy:

Using two existing Rules-Based Medicine Multi-analyte Profile (MAP) panels comprising 267 markers (DiscoveryMAP and OncologyMAP), SMA and control plasma samples collected from the BforSMA study were analyzed to identify novel plasma protein biomarker candidate hits that correlate to the Modified Hammersmith Functional Motor Scale (MHFMS) measure of disease severity in SMA patients. New immunoassays for the best hits identified by LC/MS that were not in existing MAPs were also developed.

# Results

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# Results

### Table 1: LC/MS Plasma Protein Hitlist

<ul> <li>Motos</li> <li></li></ul>	PROTEIN	DESCRIPTION	Q-VALUE
PMB         Constrained Science         Constrained Science         Constrained Science         Constrained Science           ADAMTRIA         Constrained Science         Constrained Science         Constrained Science         Constrained Science           ADAMTRIA         Constrained Science         Constrained Science         Constrained Science         Constrained Science           ADAMTRIA         Constrained Science         Constrained Science         Constrained Science         Constrained Science           ADAMTRIA         Constrained Science         Constrain	CILP2	CARTILAGE INTERMEDIATE LAYER PROTEIN 2	<0.001
0.10019         0.1001           0.1001         0.10010           0.10010 <td>COMP</td> <td>CARTILAGE OLIGOMERIC MATRIX PROTEIN</td> <td>&lt;0.001</td>	COMP	CARTILAGE OLIGOMERIC MATRIX PROTEIN	<0.001
ADM/15.4         ADM/15.4         ADM/15.4         ADM/15.4           TYDR         THEAD.X REINSTON SERVICE ADMINISTER         4.001           DPM         THEAD.X REINSTON SERVICE ADMINISTER         4.001           THEAD         THEAD.X REINSTON SERVICE ADMINISTER         4.001           THEAD         THEAD.X REINSTON SERVICE ADMINISTER         4.001           DPM         THEAD.X REINSTON SERVICE ADMINISTER         4.001           DPM         THEAD.X TYDE ADMINISTER         4.001			
1998	CLEC3B	CTYPE LECTIN DOMAIN FAMILY 3, MEMBER B	<0.001
IPPE4         CONTRACTORY INTERCENT         40.001           IPPE4         CONTR	ADAMTSL4	ADAMTSLIKE 4	<0.001
Hilds         Streamy of the second seco	TNXB	TENASCIN XB (DISTINCT ISOFORM)	<0.001
CD113         CD114         CD114 <td< td=""><td>DPP4</td><td>DIPEPTIDYLPEPTIDASE 4 (CD26, ADENOSINE DEAMINASE COMPLEXING PROTEIN 2)</td><td>&lt;0.001</td></td<>	DPP4	DIPEPTIDYLPEPTIDASE 4 (CD26, ADENOSINE DEAMINASE COMPLEXING PROTEIN 2)	<0.001
000         Statustory 100         -0.001           EREAD:         Statustory 100         -0.001           EREAD:         Calculation wetter AND, Browner and 1000         -0.001           EREAD:         Calculation wetter AND, Browner and 1000         -0.001           EREAD:         Calculation wetter AND, Browner and 1000         -0.001           APCS         Calculation wetter AND, Browner and 1000         -0.001           CALCULAT         Calculation wetter AND, Browner and 10000         -0.001           CALCULAT         Calculation wetter AND, Browner and 100000         -0.001           CALCULAT         Calculation wetter AND,	THBS4	THROMBOSPONDIN 4	<0.001
<ul> <li>Interventional and a section of the se</li></ul>	CDH13	CADHERIN 13, H-CADHERIN (HEART)	<0.001
P108P108P108P109 <tr< td=""><td>OMD</td><td>OSTEOMODULIN</td><td>&lt;0.001</td></tr<>	OMD	OSTEOMODULIN	<0.001
01081         0.4000           UM         0.4001           UM         0.4001           APGS         0.4001           APGS         0.4001           C02A1         0.4002           C02A1         0.4002           C02A1         0.4002           C02A1         0.4003           C02A1         0.4004           C02A1         0.4004           C02A1         0.4004           C02A1         0.4004           C03A1         0.4004           C04A1         0.4004           C05A2         0.4004           C05A3         0.4004           C05A4         0.4004 <t< td=""><td>CRTAC1</td><td>CARTILAGE ACIDIC PROTEIN 1</td><td>&lt;0.001</td></t<>	CRTAC1	CARTILAGE ACIDIC PROTEIN 1	<0.001
LLM         LLMOONE         LLMOONE         LLMOONE         LLMOONE         LLMOONE         LLMOONE         LLMOONE         LLMOONE         LLLMOONE         LLLLLLLLLLLMOONE         LLLLMOONE <th< td=""><td>F13B</td><td>COAGULATION FACTOR XIII, B POLYPEPTIDE</td><td>&lt;0.001</td></th<>	F13B	COAGULATION FACTOR XIII, B POLYPEPTIDE	<0.001
PEPD         Output:         Description           APCS         Automation         Automation         Automation           D10010         Automation         Automation         Automation         Automation         Automation           D10010         Automation	C1QR1	COMPLEMENT COMPONENT 1, Q SUBCOMPONENT, RECEPTOR 1	<0.001
APCS         xxvvvoc P caskrown, sexual         <5.001	LUM	LUMICAN	<0.001
60.241         00.3679, YPE IL ALENE I PERSONE OFFICIALINE SECONDARY CONSTITUTIONS OF EXAMPLE SUBJECTIONS OF EXAMPLE         40.001           NDY         VERTIONS OF EXAMPLE         40.001           COLAS         COLASSE         40.001           COLAS         COLASSE         COLASSE         40.001           COLAS         COLASSE         COLASSE         00.002           COLAS         COLASSE         COLASSE         00.002           SIN         COLASSE         COLASSE         00.002           VIN         VERTION COLASSE         00.002         00.002           VIN         VERTION COLASSE         00.003         00.004           VIN         VERTION COLASSE         00.003         00.004           ALPL         ALASSE         00.004         00.004           REGRAM         COLASSE         00.004         00.004           REGRAM		PEPTIDASE D	
NOV         Numerican Constraints of Manual Constraints of Manual Constraints         44.001           CORA         Manual Constraints         COR         Manual Constraints         COR         40.001           CORA         Constraints			
C28         NELL COMMULATION         C40.001           COLEAJ         COLUMANT MY, APRILA         0.001           CRAP         CREATORY MERTINE, NERRINE,			
COLERS         COLUMENT, TYPE VI, APPEN 3         D.001           CRP         CREATED FROME, TYPE VI, APPEN 3         D.002           VTN         VITRONECTIN (GERMA SPECIALINE FROME, TRADIT, APPENDAMENT AFD)         D.002           SSN         EXECUTE ALL COLUMNES ACCOLUMNES FROME, TRADIT, APPENDAMENT AFD)         D.003           VTN         VITRONECTIN (GERMA SPECIALINE FROME TRADIT, APPENDAMENTALINE, COMPANIE)         D.003           HBR         WITRONECTIN (GERMA SPECIALINE ALL COLUMNES), COLUMNES, COLUMNE			
CRP         Cenerative Proteins, Pertrawalesa and UTVN         0.002           VTN         UTDORECTIN (SERUM SERVACION, COMPORTEM, CONTENUE SERVICE)         0.002           VTN         UTDORECTIN (SERUM SERVACION, COMPORTEM, CONTENUE SERVICE)         0.003           VTN         UTDORECTIN (SERUM SERVACION, COMPORTEM, CONTENUES SERVICE)         0.003           APDA         INSTRUMENTING (SERUM SERVACION, COMPORTEMENT SERVICE)         0.003           APDA         ARUMAL E INSTRUMENTING (SERUM SERVACION, COMPORTEMENT SERVICE)         0.004           APDA         ARUMAL E INSTRUMENTING (SERUM SERVACION)         0.004           APDA         ARUMAL E INSTRUMENTING (SERUM SERVACION)         0.004           REGERA         EDETROVACION OF (SERUM ATMINITURI, SECTORED (SERUM)         0.004           REGERA         EDETROVACION OF (SERUM)         0.005           REGERA         EDETROVACION OF (SERUM)         0.005           REGERA         EDETROVACION OF (SERUM)         0.005			
VTN         VITROBUCTIN (IMPLUX SPRACING, RALTOR, ROLATOUR B, DOWN FURTH SPROTTIN)         0.002           CSN         BIRBIDI, MARINES, FORDER, F			
GSN         0.0033         0.0033           VTN         VTRORECTIN, (GERUA ENGEDING FACTOR, SOMEWORK) (UNITEDENT SOMEWORK)         0.003           AUPL         a visi pri mognaturicentri Somework         0.003           APDA4         a visi pri mognaturicentri Vision         0.003           APDA4         a visio pri mognaturicentri Vision         0.003           APDA4         avisio pri mognaturicentri Vision         0.003           APDA4         avisio pri mognaturicentri Vision         0.004           REGRAA         Forescontent or logi Lox antimographic (Teles)         0.004           REGRA         contention of logi Lox antimognation         0.004           REGRA         contention of logi Lox antimognation (Telescontent C2B)         0.004           REGRA         contention of logi Lox antimognation (Telescontent C2B)         0.005           RESZ/A         Languitri vision (Telescontent C2B)         0.006           RESZ/A         Languitri vision (Telescontent C2B)         0.006           RESZ/A         Languitri vision (Telescontent Contentioned Contention (Contentioned Contentioned Contention (Contentioned Contention (Contentioned Contention (Contention Contention Contention (Contention Contention (Contention Contention (Contention Contention (Contentione			
VTN         VITACING (SERUE SPACEAGE SPACEAGE SPACEAGE SPACEAGE SPACEAGE RECORD, BUERK         0.003           HBB         Incoloution (Buerk         0.003           APDAK         Assume recommentary, transformation (Serue)         0.003           PCGRIA         PE reacture recommentary, transformation (Point)         0.003           FCGRIA         Personant (Call)         0.004           FCGRIA         Personant (Call)         0.004           C205         Control (Call Server)         0.004           C205         Control (Call Server)         0.004           C206         Control (Call Server)         0.004           C207         Control (Call Server)         0.004           C208         Control (Call Server)         0.004           C209         Control (Call Server)         0.005           C210         Control (Call Server)         0.006           C211         FE Server)         0.006           C211         FE Server)         0.006           C211         FE Server)         0.006           FE Se			
HBB         HERKOLGENI, INF.         0.003           ALPL         ALKALIE PROFINATAGE LICE/REDICINENTY         0.003           APOM         ARRAUEL PROFINATAGE LICE/REDICINENTY         0.004           APOM         REDICINE PROFINATAGE LICE/REDICINENTY         0.004           FCORBA         FCORBANDER LICE         0.004           NEOT         NEOD CONCELENT C228         0.004           C28         NEOD CONCELENT C228         0.004           C750         CONCELENT C228         0.004           C752         CONCELENT C28         0.005           C75         CONCELENT C288         0.005           C75         CONCELENT C000000011         0.006           C76         HERDIC DELENT C000000000000000000000000000000000000			
ALPL         AKAI BE PROSINATASE, LIVERINGUERIONER, AV         0.003           APQAH         Anguingenettia, AV         0.004           APQAH         PC PRADMEND OF IGS, LIVER APRILLING, RESPOND (CDER), AV         0.004           NE01         NE04 PROVINCE, LIVER APRILLING, LIVERAND, CDER         0.004           NE01         NE04 PROVINCE, LIVERAND, LIVERA			
APOAL         and sequences         and sequences         0.004           FGERA         FCERAGUERI CHOS, LOW ARRENT CHOR, LOW ARRENT CHOS, LOW ARRENT CHOS, LOW ARRENT CHOS, LOW			
FCGR3A         FC PRADMENT OF IG. (DN APPINTY III, RECEIPTOR (CD15A)         0.004           NEG1         Receiver and the intervention of indexes with the indexes with			
NE01         NEDDENN HOUGUE 1 (HOLD)         0.004           C2B         MARE DECAMPLEMENT C2B         0.094           LENGT         LEUREN DO LIVERS ON APPENDING         0.006           CTSD         CATHERIAN D (LYSDEOMAL ASPARTINE HOPTIDAS)         0.006           C2         COMPLEMENT COMPONENT 2         0.006           RPS27A         UBIGUITIN AID REGORDAL ASPARTINE HOPTIDAS)         0.006           IF         Invator (Complement 2)         0.006           IF         Invator (Complement 2)         0.006           IF         Invator (Complement 2)         0.006           INFIRE         Concountion Fractor SUID AT Invator (Complement 2)         0.008           INFIRE         Concountion Fractor SUID AT Invator (Complement 2)         0.009           CP         Concountion Fractor (Complement 2)         0.0010           AGA         Asserting Element 2000 AND AND ELEMENT COMPONENTS 2)         0.013           FIBAT         Converting Element 2000 AND AND ELEMENT COMPONENTS 2)         0.013           FIBAT         Element 2)         0.013         0.			
C2B         NKED COMPLEXENT C2B         0.004           LEGT         LECTENEICH ALTH-AQUICONNOTERI 1         0.006           C1SD         COMPLEXENT CATHON AND TO COMPLEXENT CATHONARY 1         0.006           C2         COMPLEXENT CATHONARY 1         0.006           RPS2/A         LIGUITH NID BIODOMAL PROTEIN SZA PRECURSOR         0.006           IF         CELECTRIC COMPLEXENT         0.006           IGFBP6         INBUC         0.007           INMBC         COMPLEXENT         0.008           INGED         INBUC         0.008           INGED         COMPLEXENT         0.008           INGED         COMPLEXENT         0.008           INGED         COMPLEXENT         0.008           NCAM1         NEURAL CLI ADIESON MOLECULE 1         0.009           NCAM1         NEURAL CLI ADIESON MOLECULE 1         0.009           CP         COMPLEXENT 4         0.012           C9         COMPLEXENT 4         0.012           C9         COMPLEXENT 4         0.018           SPP1         SECRETED PHOSIMPORITOIN 1 (DETEORORITIN, ENEL SELOPROTEIN L EARLY TUNEHOUTH ALTINK         0.018           CM2         COMPLEXENT 4         0.020           MRC2         COMPLEXENT 4			
LRG1         LEUGNENCH ALPHAQUICORNOTEIN 1         0.004           CTSD         CATTLERIN D (UNSDEWAL APPRITM. PERTIDAE)         0.006           G2         COMPLEXENT COMPOSITY         0.006           RPS27A         URIGUITIN AND RECOMMENT PROTEIN S27A PRECURSOR         0.006           IF         Incontrol (COMPLEXENT)         0.006           IF         Incontrol (COMPLEXENT)         0.006           INFBC         Inselluntuk E AROWTI (ACTOR BLOOK RECOME LEVENT)         0.008           INFBC         Inselluntuk E AROWTI (ACTOR BLOOK RECOME LEVENT)         0.009           NCAM1         COAGULATION FAILTON XIII, APPLYPTIDE         0.009           NCAM1         COAGULATION FAILTON XIII, APPLYPTIDE         0.009           CP         CERLUCTU-SAININ (FERTONDARE)         0.010           AGA         APPLYPTIDE         0.0012           CG3         COMPLEXENT VERTONDARE)         0.0112           CG4         COMPLEXENT VERTONDARE)         0.016           LEGG1         ELEVENENCE PRODUCTURANT VERTONDARE)         0.018           SPF1         SECRETED PROSENEDENT 1 (DETEORONTIL, GAUE ALPHARTING LEUCINERICH REPAT         0.018           SILR         INMUNICOLOBULIN SUFERFAILLY CONTINUES 1         0.018           SILR         INMUNICOLOBULIN SUFERFAILLY CONTINUE			
CTSD         CATHEPISN D. (VS0050MAL ASPARTYL PEPTINASE)         0.006           C2         COMPLEMENT COMPLEMENT 2         0.006           RPS27A         UBRUITIN AND RIDSONAL PROTEIN SZ7A PRECURSOR         0.006           IF         CELEMENT AND RIDSONAL PROTEIN SZ7A PRECURSOR         0.006           IGFERE         INSULINUE GROWTH FACTOR BRIONG PROTEIN G         0.006           INHEC         CARADIA AND RIDSONAL PROTEIN SZ7A PRECURSOR         0.006           INHEC         INSULINUE GROWTH FACTOR BRIONG PROTEIN G         0.008           INHEC         COMULATION PROTEINS GROWTH FACTOR BRIONG PROTEINS G         0.009           NEURAL CELL AND RIDSON MOLECULE 1         0.009         0.009           NEURAL CELL ADDRESION MOLECULE 1         0.009         0.012           CP         CORDULATION FACTOR BRIONE PROTEINS GROWTH A DOLTA         0.012           CG         CORDULATION FACTOR COMPLEMENTS         0.012           CG         CORDULATION FACTOR COMPLEMENTS         0.012           CG         CORDULATION FACTOR COMPLEMENTS         0.013           IBBA1         LEDICINERICI ADDRESINANT A FINA         0.018           CF         ECERTED PROSENDERDED IN 1 (DSTEOPONTME, EDIC EXTORTINI THONOLT COMPONITINI 1)         0.018           CKM         CORDULATION FACTOR CONTANTINI 1)         0.01			
C2         COMPLEMENT COMPONENT 2         0.006           RPSZ7A         UBRQUITIN ADD RIGSOMAL, PROTEINS S27A, PRECURSOR         0.006           IF         IFACTOR (COMPLEMENT)         0.006           IGFBP6         INULIAUEL GROWTH PACTOR SIMINA PROTEINS 6         0.006           INHEC         INULIAUEL GROWTH PACTOR SIMINA PROTEINS 6         0.006           INHER         COMULATION FACTOR SIMINA PROTEINS 6         0.008           F13A1         COMULATION FACTOR SIMINA PROTEINS 6         0.009           CP         COMULATION FACTOR SIMINA PROTEINS 6         0.0010           ASBARTI OLICOSAMINIMASE         0.0110         ASBARTI OLICOSAMINIMASE         0.012           GS         COMMELINENT FACTOR SIMINA PROTEINS 1         0.016         0.013           HBA1         HEMOGLION SUBJINIT ALPHA         0.016         0.018           GRG1         LILCURRECEL ALPHESION MOREONENT 9         0.0113         0.018           GRG1         LILCURRECEL ALPHESION MOREONENTY 10.0118         0.018         0.018           GRG1         LILCURRECEL ALPHESION MOREONENTY 10.0018         0.013         0.018           GRG1         LILCURRECEL ALPHESION MOREONENTY 10.0018         0.013         0.018           GRG1         LILCURRECEL ALPHESION MOREONENTY 10.0018         0.018			
RPS27A         UBDUITH AND RBOSDMAL PROTEIN S27A PRECURSOR         0.006           IF         IFACTOR (COMPLEXENT)         0.006           IGFBP6         INSULINUER GROWTH PACTOR RINDING PROTEIN 6         0.008           INHEC         Insulinuer GROWTH PACTOR XIII, AT POLYPETIDE         0.009           NCMM1         COAGULATION FACTOR XIII, AT POLYPETIDE         0.009           OCM         RELIAR CELL ADRESION MOLECULE 1         0.009           AGA         COMPLEXINGLY CELL ADRESION MOLECULE 1         0.0012           CP         CERLICIDAL SAMINGER CELL ADRESION MOLECULE 1         0.0101           AGA         COMPLEXINGLY CELL ADRESION MOLECULE 1         0.0112           C9         COMPLEXINGLY CELL ADRESION MOLECULE 1         0.0113           HBA1         CEMPLEXINGLY CELL ADRESION MOLECULE 1         0.0113           LEGGI         LEGUENCERIA LARENT COLORANINADE         CEMPLEXINGLY CENTRINI 1         0.0118           SPP1         SECRETED PROSPROPROTEIN 1 (DETEOPONTINI, BONE SIALOPROTEIN 1, ALEXIN 40000         0.0121           CKM         CELEVENCERIA LARENT CANAREND REPART         0.0101           JELER         MANINOGE GREFEROR, CELER PERSINEL REPART         0.0118           SPP1         SECRETED PROSPROPADITION 1 (DETEOPONTINI, BONE SIALOPROTEIN 1, ALEXIN 4000018         0.0118			
IF         IFACTOR (COMPLEMENT)         0.006           IGFBP6         INSULINI KE GROWTH FACTOR RUNDING PROTEIN 6         0.008           INHBIC         INHBIN, BETA C         0.008           INHBIC         INHBIN, BETA C         0.009           INHBIC         COAGULATION FACTOR RUNDING PROTEIN 8         0.009           NCAMI         COAGULATION FACTOR RUNDING PROTEIN 1         0.009           NCAMI         COAGULATION FACTOR RUNDING PROTEIN 1         0.0010           AGA         COMPLEXITY COMPORTS         0.0112           G9         COEMULATION FACTOR RUNDINGSE         0.0112           G9         COMPLEXITY COMPORTS         0.0113           HBA1         HEMOGLOBIN SUBJINIT ALPHA         0.018           LEGS1         LELIONARIGON AURI-RELIVORPORTS         0.0113           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BORE SALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         0.018           CKM         CREATINE KINASE, MUSICE         0.0113           ISLR         IMMUNOCIDOULIN SUPERFAILLY CONTAINING LEUCINERICH REPART         0.0119           PRG4         CREATINE KINASE, MUSICE         0.021         0.0221           CA2         CREATINE KINASE, MUSICE         0.0237           OSCN8         OURESCIN CO COMPLEXENT KINASE III 0.			0.000
INHBC         INHBR, BETA C         0.008           F13A1         COAGULATION FACTOR XIII, A1 POLYPEPTIDE         0.009           NCAM1         MEURAL CELL ADESIGN NOLECULE 1         0.009           NCAM1         CERUICPLASMIN (FEROMOLASE)         0.010           AGA         ADEMATYI GLUCORAMINOSE         0.012           C9         COMPLEMENT COMPONENT 9         0.013           HBA1         HEMOGI GORN SUMUNT ALPIA         0.016           LRG1         ELEUCENERICH ALPHA 20LYCOPROTEIT 1         0.018           SEPP1         SECRETED PHOSPHOPROTEIN 1 (DSTEOPONTIN, BONE SINLOPROTEIN L, EARLY TURMHCOTTE ACTIVATION 1)         0.018           CKM         CREATINE KINASE, MUSCLE         0.013           INMINOGLORULIN SUPFREAMILY COMPANDED TE ACTIVATION 1)         0.018           CKM         CREATINE KINASE, MUSCLE         0.018           CKM         CREATINE KINASE, MUSCLE         0.018           MRC2         MANNOGLORULIN SUPFREAMILY COMPANDED TE ACTIVATION 1)         0.019           MRC4         MANNOGLORULIN SUPFREAMILY COMPANDED TE ACTIVATION 1)         0.029           PRO4         CREADINC AND VILLA         0.021         0.025           GSCN6         GUEGON OG         0.029         0.025           SOSCN6         CARBONIC AND VILLA		UBIQUITIN AND RIBOSOMAL PROTEIN S27A PRECURSOR	0.006
F13A1         COAGULATION FACTOR XIII, A1 POLYPEPTIDE         0.009           NCAM1         NEURAL CELL ADESIGN MACECULE 1         0.009           CP         CERULOPLASMIN (FERROXDASE)         0.0101           AGA         APARTYLIQUEOSAMINOSE         0.012           C9         COMPLEMENT COMPONENT 9         0.0131           HBA1         COMPLEMENT COMPONENT 9         0.013           HBA1         HEMOGLOBIN SUBURIT ALPHA         0.016           LRG1         COMPLEMENT COMPONENT 9         0.018           SPP1         SECRETED PHOSPHOPROTEIN I (DISTEOPONTIN, BONE SIALOPROTEIN I ALPLAZ (LYCOPROTEIN 1         0.018           CKM         CREATINE KINASE, MUSCLE         0.019           PRG4         CONCURST EXTRUSTING EN CERTINE RUNASE, MUSCLE         0.019           PRG4         PROTEOLYCAN 4         0.020           GA2         CARBONIC ANHYDRASE II         0.021           CAA2         CARBONIC ANHYDRASE II         0.0225           QSCN6         GUILESCIN Q6         0.029           PRG4         CARBONIC ANHYDRASE II         0.037           CST6         GUILESCIN Q6         0.037           SSCN6         GUILESCIN Q6         0.037           S1000 CALCIUM BINDING PROTEIN A (CALCIUM FROTEIN, CALVASCULIN, METRE FLACENTAL H			
NCAM1         NEURAL CELL ADESION MOLECULE 1         0.009           CP         CERILOPLASMIN (FERROXIDASE)         0.010           AGA         ASPARTYLGLUCOSMININASE         0.012           C9         COMPLEMENT COMPONENT 9         0.013           HBA1         COMPLEMENT COMPONENT 9         0.016           LRG1         LEUCINERICH ALPHA2GLYCOPROTEIN 1         0.018           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         0.018           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         0.018           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         0.018           CKM         CREATINE KINASE, MUSCLE         0.018           JBLR         IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICAL REPEAT         0.019           PRG4         CREATINE KINASE, MUSCLE         0.018           JBLR         IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICAL REPEAT         0.020           MRC2         MANNOSE RECEPTOR, C TYPE 2         0.021           CA2         CAROBING CONTAINING LEUCINERICAL REPEAT         0.025           QSCN8         QUESCN OG         QUESCN OG         0.027           PRC4         PR	IF	I FACTOR (COMPLEMENT)	0.006
CP         CERULOPLASMIN (FERROXIDASE)         0.010           AGA         ASPARTYLGLICOSAMINIDASE         0.012           C9         COMPLEMENT COMPONENT 9         0.013           HBA1         COMPLEMENT COMPONENT 9         0.013           HBA1         ELGOIRECT COMPONENT 9         0.013           LRG1         LEUCINEERIC LIPHASQL/COORDENT 1         0.016           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN I, EARL'T LYMPHOZYTE ACTIVATON 1)         0.018           CKM         CREATINE KINASE, MUSCLE         0.018           ISLR         CREATINE KINASE, MUSCLE         0.019           PRG4         PROTEOGLYCAN 4         0.020           MRC2         MANINOSE RECEPTOR, C TYPE 2         0.021           CA2         QUESCIN CA         0.025           QSCN6         QUESCIN CA         0.037           PRC4         QUESCIN CA         0.037           S100A1         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HONOLOG         0.037           S100A1         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HONOLOG         0.037           SERPINA10         SERPIN PEPTIDASE INHEITOR, CLADE A (ALIPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10         0.037	IF IGFBP6	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6	0.006 0.006
AGA         ASPARTYLGUCOSAMINIDASE         0.012           C9         COMPLEMENT COMPONENT 9         0.013           HBA1         COMPLEMENT COMPONENT 9         0.013           HBA1         HEMOGLOBIN SUBURIT ALPHA         0.016           LIRG1         LEUCINERICH ALPHA2GLYCOPROTEIN 1         0.018           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPTOTI, LEALY, TVMPHOCYT EATUNATION 1)         0.018           CKM         CREATINE KINASE, MUSCLE         0.019           PR64         PROTEOCLYCAN 4         0.020           MRC2         MANNOSE RECEPTOR, C TYPE 2         0.021           CA2         CARBOINC ANIVORASE II         0.025           QSCNB         QUIESCIN QG         0.029           PROC         PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIILA)         0.037           PGK1         PHOSPHOGLYCERATE KINASE 1         0.037           S10044         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG         0.037           SERPIN PEPTIDASE INHIBITOR, CLAVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG         0.037           S100A4         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG         0.037           SERPIN PEPTIDASE INHIBITOR, CLAVASCULIN, METASTASIN, MURINE PLACENTAL	IF IGFBP6 INHBC	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C	0.006 0.006 0.008
C9         COMPLEMENT COMPONENT 9         0.013           HBA1         HEMOGLOBIN SUBUNIT ALPHA         0.016           LRG1         LEUCINERICH ALPHAZGLYCOPROTEIN 1         0.018           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EALLY TLYMPHOCYTE ACTIVATION 7)         0.018           CKM         CREATINE KINASE, MUSCLE         0.019           PRG4         CREATINE KINASE, MUSCLE         0.020           MRC2         PROTEOSLYCON4         0.020           MRC2         CARBONIC ANHYDRASE II         0.025           QSCN6         QUESCN6         QUESCN6           PROC         PROTEOSLYCON4         0.027           PRG4         CARBONIC ANHYDRASE II         0.025           QSCN6         QUESCN6         QUESCN 6           PROC         PROTEOSLYCON4         0.037           S100A4         S100 CALCIUM BINDING PROTEIN AL (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.037           S100A4         S100 CALCIUM BINDING PROTEIN AL (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.039           ENG         CVESTATIN E/M         0.042         0.042           PARK7         SERPIN PEPTIDASE INHIBITOR, CLAUPASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.039	IF IGFBP6 INHBC F13A1	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE	0.006 0.006 0.008 0.009
HBA1         HEMOGLOBIN SUBUNIT ALPHA         0.016           LRG1         LEUCINERICH ALPHA2GLYCOPROTEIN 1         0.018           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         0.018           CKM         CREATINE KINASE, MUSCLE         0.019           PRG4         ROTORIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         0.020           MRC2         PROTEORLYCAN 4         0.020           MRC2         MANNOSE RECEPTOR, C TYPE 2         0.021           CA2         CARBONIC AMMYDRASE II         0.025           QSCN6         QUIESCIN Q6         0.029           PROC         CARBONIC AMMYDRASE II         0.037           PGK1         PHOSPHOGLYCERATE KINASE 1         0.037           S100A4         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.037           S100A4         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOGO         0.039           ENG         ENDOGLIN COLLER RENDUWEBER SYNDROME 1)         0.042           PARK7         SERPIN PEPTIDASE INHIBITOR, ICALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOGO         0.039           ENG         ENDOGLIN COLLER RENDUWEBER SYNDROME 1)         0.042           PARK	IF IGFBP6 INHBC F13A1 NCAM1	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1	0.006 0.006 0.008 0.009 0.009
LRG1         LEUCINERICH ALPHA2GLYCOPROTEIN 1         0.018           SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         0.018           CKM         CREATINE KINASE, MUSCLE         0.018           ISLR         IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT         0.019           PRG4         PROTEORYCAN 4         0.020           MRC2         CARBONIC ANHYDRASE II         0.025           QSCN6         QUIESCIN Q6         0.029           PROC         CARBONIC ANHYDRASE II         0.037           PGK1         O.037         0.037           S100A4         S100 CALCIUM BINDING PROTEIN AL (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.037           S100A4         S100 CALCIUM BINDING PROTEIN AL (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.039           ENG         CYSTATIN E/M         0.037           SERPIN PEPTIDASE INHIBITOR, CLADE A (LALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10         0.039           ENG         ENDOGLIN (OSLERRENDU/WEBER SYNDROME 1)         0.042           PARK/7         CACADE ALAPHA I ANTIPROTEINASE (ALTOSOMAL RECESSINE, EARLY ONSET) 7         0.042           VCAM1         VASCULAR CELL ADHESION MOLECULE 4         0.055           MET <td< td=""><td>IF IGFBP6 INHBC F13A1 INCAM1 CP I</td><td>I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE)</td><td>0.006 0.006 0.008 0.009 0.009 0.010</td></td<>	IF IGFBP6 INHBC F13A1 INCAM1 CP I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE)	0.006 0.006 0.008 0.009 0.009 0.010
SPP1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         0.018           CKM         CREATINE KINASE, MUSCLE         0.019           ISLR         IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT         0.019           PRG4         PROTEOGLYCAN 4         0.020           MRC2         CARBONIC ANHYDRASE II         0.025           CA2         CARBONIC ANHYDRASE II         0.029           PROC         QUIESCIN Q6         0.029           PROC         PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)         0.037           PGK1         OLO37         CST6         CYSTATIN E/M         0.037           S100A4         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.037           S100A4         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.037           SERPINA10         SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPIN), MEMBER 10         0.032           ENG         ENDOGLIN (OSLERRENDUWEBER SYNDROME 1)         0.042           VCAM1         MET PROTOONCOCOEKE (HEPATOCYTE GROWTH FACTOR RECEPTOR)         0.055           PEBP4         MET PROTOONCOCOEKE (HEPATOCYTE GROWTH FACTOR RECEPTOR)         0.056           ORM2	IFIGFBP6INHBCF13A1NCAM1CPAGA	I FACTOR (COMPLEMENT)         INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6         INHIBIN, BETA C         INHIBIN, BETA C         COAGULATION FACTOR XIII, A1 POLYPEPTIDE         NEURAL CELL ADHESION MOLECULE 1         CERULOPLASMIN (FERROXIDASE)         ASPARTYLGLUCOSAMINIDASE	0.006 0.006 0.008 0.009 0.009 0.010 0.012
CKM         CREATINE KINASE, MUSCIE         0.018           ISLR         IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT         0.019           PRG4         PROTEOGLYCAN 4         0.020           MRC2         MANNOSE RECEPTOR, C TYPE 2         0.021           CA2         CARBONIC ANNYDRASE II         0.025           QSCN6         QUIESCIN C6         0.029           PROC         PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)         0.037           PGK1         O.037         PHOSPHOGLYCERATE KINASE 1         0.037           S100A4         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.037           S100A4         S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)         0.037           SERPINA10         SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPOTEINASE, ANTITRYPSIN), MEMBER 10         0.039           ENG         ENDOGLIN (OSLERRENDUWEBER SYNDROME 1)         0.042           VCAM1         VASCULAR CELL ADHESION MOLECULE 1         0.055           PEBP4         MET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)         0.056           ORM2         OROSOMUCOID 2         0.0600           ORM2         OROSOMUCOID 2         0.0660           CANDPI	IFIGFBP6INHBCF13A1NCAM1CPAGAC9	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9	0.006 0.006 0.008 0.009 0.009 0.010 0.012 0.013
ISLRIMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT0.019PRG4PROTEOGLYCAN 40.020MRC2MANNOSE RECEPTOR, C TYPE 20.021CA2CARBONIC ANHYDRASE II0.025QSCN6QUIESCIN Q60.029PROCPROTEOGLYCAN 40.037PGK1PHOSPHOGLYCERATE KINASE I0.037CST6CYSTATIN E/M0.037S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)0.037SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE Á (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGENDOGLIN (OSLER RENDUWEBER SYNDROME 1)0.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.056PEBP4OROSOMUCOLO 20.0600CNDP1CARDONICAGIDA E ACCANTANTING PENTIDASE 1 (METALLOPEPTIDASE 1 METALLOPEPTIDASE M20 FAMILY)0.066FIAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIGFBP6INHBCF13A1NCAM1CPAGAC9HBA1	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) CERULOPLASMIN (FERROXIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA	0.006 0.006 0.008 0.009 0.009 0.010 0.012 0.013 0.016
PRG4PROTEOGLYCAN 40.020MRC2MANNOSE RECEPTOR, C TYPE 20.021CA2CARBONIC ANHYDRASE II0.025QSCN6QUIESCIN Q60.029PROCPROCPROTEINC (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)0.037PGK1PHOSPHOGLYCERATE KINASE 10.037CST6CYSTATIN E/M0.037S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)0.039SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039FNGCYSTATIN E/M0.042VCAM1CARDOSINE INFERTION DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055PEBP4OROSOMUCOID 20.050ORM2OROSOMUCOID 20.060CNDP1CARNOSINE DIPEPTIDASE I (METALLOPEPTIDASE I (METALLOPEPTIDASE I METALOPEPTIDASE I (METALLOPEPTIDASE I METALOPEPTIDASE I (METALLOPEPTIDASE I AUTOSOMUCOID 2FAPFIBROBLAST ACTIVATION PROTEINA, ALPHA0.066	IFIGFBP6INHBCF13A1F13A1NCAM1CPAGAC9HBA1LRG1SPP1	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1	0.006 0.006 0.008 0.009 0.009 0.010 0.012 0.013 0.016 0.018
MRC2MANNOSE RECEPTOR, C TYPE 20.021CA2CARBONIC ANHYDRASE II0.025QSCN6QUESCIN QG0.029PROCOUESCIN QG0.029PROCPROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)0.037PGK1PHOSPHOGLYCERATE KINASE I0.037CST6CYSTATIN E/A0.037S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)0.039SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGSERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.042PARK7OORD20.0420.045METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.055PEBP4OROSOMUCOID 20.0600.056ORM2OROSOMUCOID 20.0600.066FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIGFBP6INHBCF13A1F13A1CPAGAC9HBA1LRG1SPP1CKM	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)	0.006 0.008 0.009 0.009 0.010 0.012 0.013 0.013 0.016 0.018 0.018 0.018
CA2CARBONIC ANHYDRASE II0.025QSCN6QUIESCIN Q60.029PROCPROCPROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)0.037PGK1PHOSPHOGLYCERATE KINASE I0.037CST6CYSTATIN E/M0.037S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)0.037SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGENDOGLIN (OSLERRENDUWEBER SYNDROME 1)0.042PARK7PARKINSON DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.055PEBP4OROSOMUCID 20.060CNDP1CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)0.066FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIIGFBP6IINHBCIF13A1INCAM1ICPIAGAIC9IHBA1ILRG1ISPP1ICKMIISLRI	I FACTOR (COMPLEMENT)         INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6         INHIBIN, BETA C         INHIBIN, BETA C         COAGULATION FACTOR XIII, A1 POLYPEPTIDE         NEURAL CELL ADHESION MOLECULE 1         CERULOPLASMIN (FERROXIDASE)         CERULOPLASMIN (FERROXIDASE)         COMPLEMENT COMPONENT 9         COMPLEMENT COMPONENT 9         HEMOGLOBIN SUBUNIT ALPHA         LEUCINERICH ALPHA2GLYCOPROTEIN 1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN I, EARLY TLYMPHOCYTE ACTIVATION 1)         CREATINE KINASE, MUSCLE	0.006 0.008 0.009 0.009 0.010 0.012 0.012 0.013 0.018 0.018 0.018 0.018 0.018
QSCN6QUIESCIN Q60.029PROCPROCPROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)0.037PGK1PHOSPHOGLYCERATE KINASE 10.037CST6CYSTATIN E/M0.037S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)0.037SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGENG0.042PARK7PARKINSON DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.056PEBP4OROSOMUCOID 20.060ORM2OROSOMUCOID 20.060CNDP1FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIIGFBP6IINHBCIF13A1IRCAM1ICPIAGAIC9IHBA1ILRG1ISPP1ICKMIISLRPRG4	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4	0.006 0.008 0.009 0.009 0.010 0.012 0.012 0.013 0.018 0.018 0.018 0.018 0.018 0.019 0.020
PROCPROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)0.037PGK1PHOSPHOGLYCERATE KINASE 10.037CST6CYSTATIN E/M0.037S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)0.037SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGENDOGLIN (OSLERRENDUWEBER SYNDROME 1)0.042PARK7PARK70.0420.055METOCASTIN EPTIDASE INHIBITOR, CLADE A (ALPHA1 CULLE ADHESION MOLECULE 1)0.055METOCASTIN EPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METOCASTIN EPTIDASE INHIBITOR, CLADE A (ALPHA1 CULLE ADHESION MOLECULE 1)0.055PEBP4OCASTIN EPTIDASE INFORMATION CORSONUCID 20.060ORM2OROSOMUCID 20.0600.060CNDP1FIBROBLAST ACTIVATION PROTEIN, ALPHA0.066FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ILRG1ISPP1ICKMIISLRPRG4MRC2I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2	0.006 0.008 0.009 0.009 0.010 0.012 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021
PGK1PHOSPHOGLYCERATE KINASE 10.037CST6CYSTATIN E/M0.037S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)0.037SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGENDOGLIN (ÖSLERRENDUWEBER SYNDROME 1)0.042PARK7PARKINSON DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.055PEBP4PHOSPHATIDYLETHANOLAMINEBINDING PROTEIN 40.058ORM2OROSOMUCOID 20.060CNDP1FIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ILRG1ISPP1ICKMIISLRIPRG4IMRC2CA2	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II	0.006 0.008 0.009 0.009 0.010 0.012 0.012 0.013 0.013 0.016 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.025
CST6CYSTATIN E/M0.037S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG)0.037SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGENDOGLIN (OSLERRENDUWEBER SYNDROME 1)0.042PARK7PARK770.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METOMET0.055PEBP4PHOSPHATIDYLETHANOLAMINEBINDING PROTEIN 40.058ORM2OROSOMUCOID 20.060FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIGFBP6INHBCF13A1F13A1CPAGACPAGAC9HBA1LRG1SPP1CKMISLRPRG4PRG4MRC2CA2QSCN6	IFACTOR (COMPLEMENT)         INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6         INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6         INHIBIN, BETA C         COAGULATION FACTOR XIII, A1 POLYPEPTIDE         COAGULATION FACTOR XIII, A1 POLYPEPTIDE         NEURAL CELL ADHESION MOLECULE 1         CERULOPLASMIN (FERROXIDASE)         ASPARTYLGLUCOSAMINIDASE         COMPLEMENT COMPONENT 9         MEMOGLOBIN SUBUNIT ALPHA         LEUCINERICH ALPHA2GLYCOPROTEIN 1         SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1)         CREATINE KINASE, MUSCLE         IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT         PROTEOGLYCAN 4         MANNOSE RECEPTOR, C TYPE 2         CARBONIC ANHYDRASE II         QUIESCIN Q6	0.006 0.008 0.009 0.009 0.010 0.012 0.013 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.025 0.029
S100A4S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG0.037SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGENDOGLIN (OSLERRENDUWEBER SYNDROME 1)0.042PARK7PARK70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMETMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.055PEBP4PHOSPHATIDYLETHANOLAMINEBINDING PROTEIN 40.058ORM2OROSOMUCOID 20.060FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIGFBP6INHBCF13A1F13A1CPAGACPAGAC9HBA1LRG1SPP1CKMISLRPRG4PRG4MRC2CA2QSCN6PROC	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FEROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II QUIESCIN Q6 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)	0.006 0.008 0.009 0.009 0.010 0.012 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.025 0.029 0.037
SERPINA10SERPIN PEPTIDASE INHIBITOR, CLADE À (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 100.039ENGENDOGLIN (OSLERRENDUWEBER SYNDROME 1)0.042PARK7PARKINSON DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET0.055PEBP4PHOSPHATIDYLETHANOLAMINEBINDING PROTEIN 40.058ORM2OROSOMUCID 20.060CNDP1CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)0.066FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ICRG1ISPP1ICKMIISLRIPRG4IMRC2IQSCN6IPRG4IQSCN6IPGK1I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INSUBIN, BETA C INSUBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPOTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN I, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE MMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II GUIESCIN Q6 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)	0.006 0.008 0.009 0.009 0.010 0.012 0.012 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.025 0.029 0.029 0.037
ENGENDOGLIN (OSLERRENDUWEBER SYNDROME 1)0.042PARK7PARKINSON DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.055PEBP4OROSOMUCOID 20.060ORM2OROSOMUCOID 20.060CNDP1CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)0.066FAPIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ICRG1ISPP1ICKMIISLRIPRG4IMRC2IQSCN6IPRG4IQSCN6IPGK1I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INSUBIN, BETA C INSUBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPOTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN I, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE MMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II GUIESCIN Q6 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA)	0.006 0.008 0.009 0.009 0.010 0.012 0.012 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.025 0.029 0.029 0.037
ENGENDOGLIN (OSLERRENDUWEBER SYNDROME 1)0.042PARK7PARKINSON DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.055PEBP4ORN2OROSOMUCOID 20.060CNDP1CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)0.066FAPIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IF         IGFBP6         INHBC         F13A1         F13A1         NCAM1         CP         AGA         C9         HBA1         LRG1         SPP1         CKM         ISLR         PRG4         QSCN6         PROC         PROC         PGK1         CST6	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FEROXIDASE) ASPARTYLGUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA CUNERICH ALPHA2GLYCOPTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN I, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II QUIESCIN Q6 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCERATE KINASE 1 CYSTATIN E/M	0.006 0.008 0.009 0.009 0.010 0.012 0.013 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.022 0.022 0.022 0.023 0.037
PARK7PARKINSON DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 70.042VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.055PEBP4PHOSPHATIDYLETHANOLAMINEBINDING PROTEIN 40.058ORM2OROSOMUCOID 20.060CNDP1CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)0.066FAPIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IF         IGFBP6         INHBC         F13A1         NCAM1         CP         AGA         C9         HBA1         LRG1         SPP1         CKM         ISLR         PRG4         MRC2         QSCN6         PROC         PGK1         CST6         S100A4	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II QUIESCIN Q6 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCERATE KINASE 1 CYSTATIN E/M \$100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG	0.006 0.008 0.009 0.009 0.010 0.012 0.013 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.021 0.025 0.029 0.025 0.029 0.037 0.037
VCAM1VASCULAR CELL ADHESION MOLECULE 10.055METMET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)0.055PEBP4PHOSPHATIDYLETHANOLAMINEBINDING PROTEIN 40.058ORM2OROSOMUCOID 20.060CNDP1CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)0.066FAPFIBROBLAST ACTIVATION PROTEIN, ALPHA0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ICRG1ISPP1IGR4IPRG4IQSCN6IPROCIPROCIPGK1ICST6S100A4SERPINA10I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II QUIESCIN Q6 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOQLYCERATE KINASE I CYSTATIN E/M S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10	0.006 0.008 0.009 0.009 0.009 0.010 0.012 0.013 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.021 0.025 0.029 0.025 0.029 0.029 0.037 0.037
MET       MET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)       0.055         PEBP4       PHOSPHATIDYLETHANOLAMINEBINDING PROTEIN 4       0.058         ORM2       OROSOMUCOID 2       0.060         CNDP1       Expression of the sector of the sec	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ISPP1ISPP1ISPP1ISPP1IGXMIGXMIPRG4IPRG4IQSCN6IPROCIPGK1ICST6S100A4ENGIENGI	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCO PROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN I, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II OUIESCIN 06 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIII)) PHOSPHOGLYCERATE KINASE, MUSCLE S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURIE, PLACENTAL HOMOLOG) SERPIN PEPTIDASE INHIBITOR, CALVASCULIN, METASTASIN, MURIE, PLACENTAL HOMOLOG SERPIN PEPTIDASE INHIBITOR, CALVASCULIN, MURIE, PLACENTAL HOMOLOG	0.006 0.008 0.009 0.009 0.009 0.010 0.012 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.025 0.029 0.025 0.029 0.029 0.037 0.037 0.037
PEBP4       PHOSPHATIDYLETHANOLAMINEBINDING PROTEIN 4       0.058         ORM2       OROSOMUCOID 2       0.060         CNDP1       CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)       0.066         FAP       OROSOMUCOID 2       0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ICSPP1ISPP1ISPP1IGXMIFRG4IPRG4IQSCN6IPROCIPROCIPROCIS100A4IENGIPARK7I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN I, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II OUIESCIN Q6 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIII)A) PHOSPHOGLYCERATE KINASE 1 CYSTATIN E/M \$100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOS) SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 ENDOGLIN (OSLERRENDU/WEBER SYNDROME 1) PARKINSON DISEASE (AUTOSOMAL RECESSIVE, EARLY ONSET) 7	0.006 0.008 0.009 0.009 0.009 0.010 0.012 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.021 0.021 0.022 0.021 0.025 0.029 0.029 0.029 0.037 0.037 0.037
ORM2       OROSOMUCOID 2       0.060         CNDP1       CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)       0.066         FAP       FIBROBLAST ACTIVATION PROTEIN, ALPHA       0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ICSPP1ISPP1ISPP1IGXAIFRG4IPRG4IPRG4IQSCN6IPROCIPROCIPROCIS100A4ISERPINA10IPARK7IVCAM1I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNT ALPHA LEUCINERICH ALPHA2GLYCOPTOTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II OUIESCIN 06 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCERATE KINASE 1 OUIESCIN 06 PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCERATE KINASE 1 CVSTATIN E/M S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG) SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 ENDOGLIN (OSLERRENDIW CONSENT) 7 PARKINSON DISEASE (ALTOSOMAL RECESSIVE, EARLY ONSET) 7 VASCULAR CELL ADHESION MOLECULE 1	0.006 0.008 0.009 0.009 0.009 0.010 0.012 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.021 0.021 0.022 0.025 0.029 0.029 0.037 0.037 0.037 0.037
CNDP1       CARNOSINE DIPEPTIDASE 1 (METALLOPEPTIDASE M20 FAMILY)       0.066         FAP       FIBROBLAST ACTIVATION PROTEIN, ALPHA       0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAICPIAGAICPIAGAICPIAGAICPIAGAICPICSPP1ICKMIFRG4IPRG4IPRG4IPRG4IPROCIPROCIPGK1IPGK1IS100A4IPARK7IVCAM1IMETI	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECUE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINIDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBURIT ALPHA LEUCINERICH ALPHA2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE IMMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEORCLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE I OULESCIN GE PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCERATE KINASE 1 CYSTATIN E/M S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTEL HIMMELOG SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPISIN), MEMBER 10 ENDOGLIN (OSLERRENDUWERE SYNDROME 1) PARKINSON DISEASE (ALTOSOMAL RECESSIVE, EARLY ONSET) 7 VASCULAR CELL ADHESION MOLECULE 1 MET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR)	0.006 0.008 0.009 0.009 0.009 0.010 0.010 0.012 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.021 0.021 0.025 0.029 0.029 0.029 0.025 0.037 0.037 0.037 0.037
FAP       FIBROBLAST ACTIVATION PROTEIN, ALPHA       0.066	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAICPIAGAICPIAGAICPIAGAICPICSP1IISLRIPRG4IPRG4IPRG4IQSCN6IPROCIPROCIPROCIPROCIPROCISERPINA10IENGIPARK7IVCAM1IPEBP4I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADMESION MOLECILE 1 CERULOPLASMIN (FERROXIDASE) ASPARTYLGLUCOSAMINDASE COMPLEMENT COMPONENT 9 HEMOGLOBIN SUBUNIT ALPHA LEUCINERICH ALPHA2GLYCOCPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN 1, EARLY TLYMPHOCYTE ACTIVATION 1) CREATINE KINASE, MUSCLE MUNINOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, C TYPE 2 CARBONIC ANHYDRASE II OULESCIN CG PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCENATE KINASE II OULESCIN CG PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCENATE KINASE II OULESCIN CG PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCENATE KINASE II OULESCIN CG PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCENATE KINASE II OULESCIN CG PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCENATE KINASE II OULESCIN CG PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCENATE KINASE II OULESCIN CG PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCENATE KINASE II OULESCIN CG MET PROTEONACIOLOGIN (SLERRENDUWBERE SYNDROME 1) PARKINGON DISEASE (ALUTOSOMIL RECESIVE, EARLY ONSET) 7 VASCULUR CELL ADMESION MOLECULE 1 MET PROTOONCOGENE (HEPATIOYLETHANOLAMINEBINDING PROTEIN 4	0.006         0.008         0.009         0.009         0.009         0.010         0.012         0.013         0.016         0.018         0.018         0.019         0.019         0.018         0.019         0.020         0.021         0.025         0.029         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.037
	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ICKMISPP1IGRG4IFRG4IPRG4IPRG4IQSCN6IPROCIPROCIPROCIPROCIPROCISERPINA10ISERPINA10IPARK7IVCAM1IPEBP4IORM2I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INHIBIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERLLOPLASINI (EERROXIDASE) CERLLOPLASINI (EERROXIDASE) COMPLEMENT COMPONENT 9 HENOCLOSIN SUBLINIT ALPHA LEUCINERICH ALPHAZGLYCORPONENT 9 HENOCLOSIN SUBLINIT ALPHA LEUCINERICH ALPHAZGLYCORPONENT 1 SEGRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN I, LEUCINERICH ALPHAZGLYCORPONENT 1 DICEATINE KINASE, MUSCL MMUNOGLOBULIN SUPERFAMILY CONTAINING LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, CTYPE 2 CARBONIC ANHYDRASE II OUIESCIN 0G PROTEIN C (INACTIVATOR OF COAGULATION FACTORS VA AND VIIIA) PHOSPHOGLYCEATE KINASE 1 CYSTATIN E/M S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOGI SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 NASOUAR ACELSING DE SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 PARKINSON DISEASE (CLADEMESING AND CLEDE 1 MET PROTOONCOCENE (HEPATCYPE GROWTH FACTOR RECEPTOR) T VASOUAR ACEL ADHESION MOLECULE 1 MET PROTOONCOCENE (HEPATCYPE GROWTH FACTOR RECEPTOR) T PHOSPHADILYCETHANDLAMINEBINDING PROTEIN 4 OROSOMUCOID 2	0.006 0.008 0.009 0.009 0.009 0.010 0.010 0.012 0.013 0.013 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.019 0.020 0.021 0.021 0.025 0.029 0.029 0.029 0.029 0.037 0.037 0.037 0.037 0.037 0.037 0.037
	IFIIGFBP6IINHBCIF13A1ICPIAGAICPIAGAIC9IHBA1ICKMISPP1IGRG4IFRG4IPRG4IQSCN6IPROCIPROCIPROCISERPINA10ISERPINA10IPARK7IVCAM1IPEBP4IORM2IORM2IORM2I	I FACTOR (COMPLEMENT) INSULINLIKE GROWTH FACTOR BINDING PROTEIN 6 INMEIN, BETA C COAGULATION FACTOR XIII, A1 POLYPEPTIDE NEURAL CELL ADHESION MOLECULE 1 CERLIOPLASINI, ICERROXIDASE CERLIOPLASINI, ICERROXIDASE COMPLEMENT COMPONENT 9 HEMOGLOSINI SUBUNIT ALPHA LEUCINERICH ALPHA/2GLYCOPROTEIN 1 SECRETED PHOSPHOPROTEIN 1 (OSTEOPONTIN, BONE SIALOPROTEIN LEUCINERICH REPEAT PROTEOGLYCAN 4 MANNOSE RECEPTOR, CTYPE 2 CARBONIC ANHYDRASE II OURSEIN CG PROTEIN C (INACTIVATOR OF COAGULATION FACTOR XV AND VIII) CREATIVE KINASE, MUSCLE SECRETED PHOSPHOPROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE FLACENTAL HOMOLOG) SECRETED PHOSPHOPROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE FLACENTAL HOMOLOG) SECRETED SPOTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE FLACENTAL HOMOLOG) SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 COYSTATIN E/M S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE FLACENTAL HOMOLOG) SERPIN PEPTIDASE INHIBITOR, CLADE A (ALPHA1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 10 ENDOGUN (OSLERRENDUWEBER SYNDROME 1) PARKINSON DISEASE (ALTOSOMAL RECESSING, EARLY ONSET) 7 VASCULAR CELL ADHESION MOLECULE 1 MET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR) PHOSPHATIDYLETHANDLAMIESING PROTEIN A1 (METALDOPEPTIDASE MOLECULE 1 MET PROTOONCOGENE (HEPATOCYTE GROWTH FACTOR RECEPTOR) PHOSPHATIDYLETHANDLAMIESING PROTEIN A1 (METALDOPEPTIDASE MOL PROTEIN A CORSOMUCCID 2 CARNOGINE DIPEPTIDASE IN (METALLOPEPTIDASE M20 FAMILY)	0.006         0.008         0.009         0.009         0.010         0.012         0.013         0.016         0.018         0.018         0.019         0.018         0.019         0.018         0.019         0.020         0.021         0.025         0.029         0.037         0.042         0.055

### Table 3: OncologyMAP Plasma Protein Hitlist

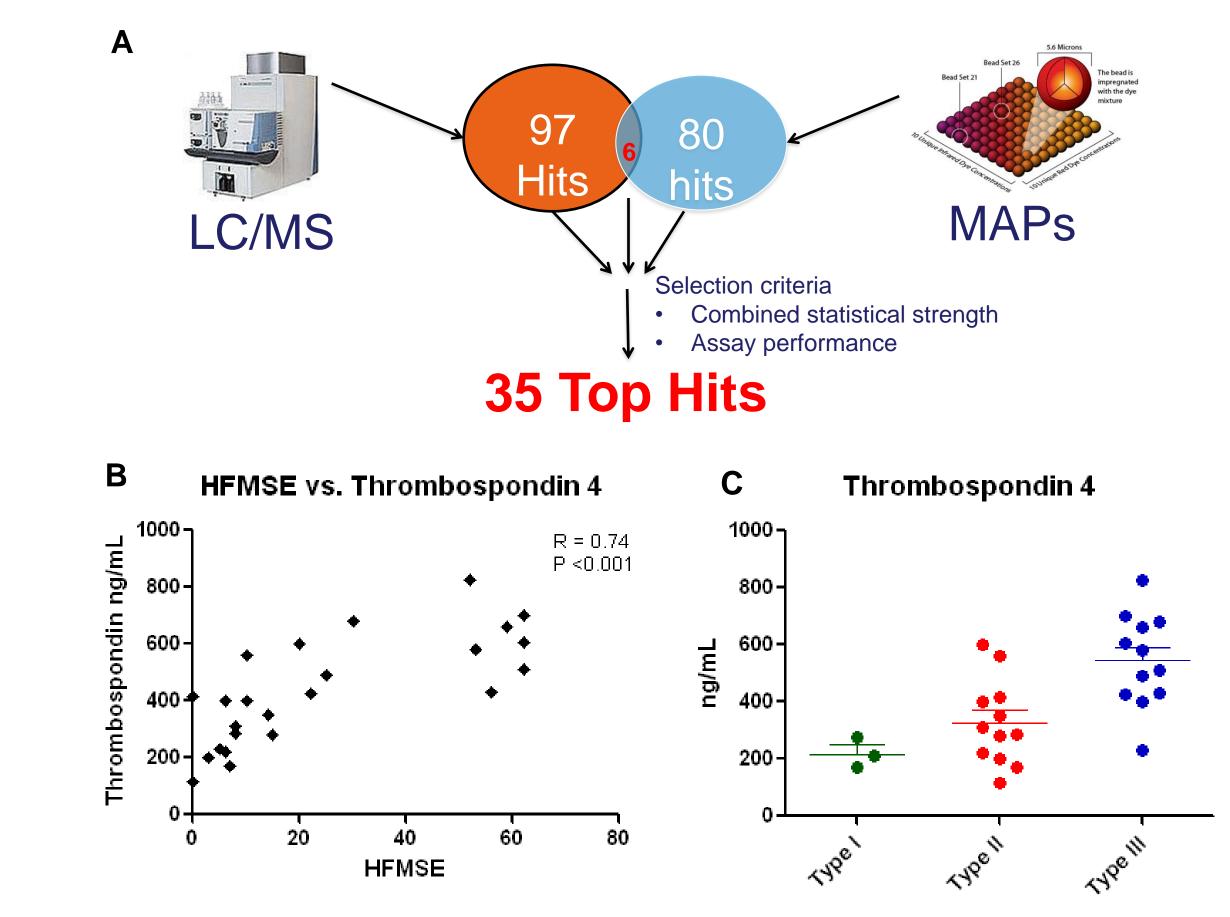
P-VALUE	DESCRPTION	PROTEIN
<0.001	OSTEOPONTIN (SECRETED PHOSPHOPROTEIN 1)	SPP1
<0.001	C-TYPE LECTIN DOMAIN FAMILY 3, MEMBER B; TETRANECTIN	CLEC3B
<0.001	INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 6	IGFBP6
<0.001	FATTY ACID BINDING PROTEIN 4, ADIPOCYTE	FABP4
<0.001	CHITINASE 3-LIKE 1 (CARTILAGE GLYCOPROTEIN-39), YKL-40	CHI3L1
<0.001	LEPTIN	LEP
0.001	CATHEPSIN D	CTSD
0.001	MACROPHAGE STIMULATING 1 (HEPATOCYTE GROWTH FACTOR-LIKE)	MST1
0.001	MACROPHAGE MIGRATION INHIBITORY FACTOR (GLYCOSYLATION-INHIBITING FACTOR)	MIF
0.001	S100 CALCIUM BINDING PROTEIN A4	S100A4
0.001	GLYOXALASE 1; LACTOYLGLUTATHIONE LYASE	GLO1
0.001	ENDOGLIN	ENG
0.002	FMS-RELATED TYROSINE KINASE 1 (VASCULAR ENDOTHELIAL GROWTH FACTOR/VASCULAR PERMEABILITY FACTOR RECEPTOR)	FTL1
0.003	HUMAN EPIDERMAL GROWTH FACTOR 2	ERBB2
0.004	NUCLEOSIDE PHOSPHATASE KINASE ISOFORM B	NDK-8
0.01	PEROXIREDOXIN 4	PRDX-4
0.015	PLASMINOGEN ACTIVATOR, UROKINASE RECEPTOR	PLAUR
0.02	INTERLEUKIN 6 RECEPTOR	IL6R
0.034	CHEMOKINE (C-C MOTIF) LIGAND 24	CCL24
0.038	Gelsolin	GSN
0.039	PHOSPHOSERINE AMINOTRANSFERASE	PSAT
0.049	TRANSFORMING GROWTH FACTOR, BETA 1, LATENCY ASSOCIATED	TGFB1

### SMA Plasma Protein Biomarker Identification and Performance

A: BforSMA plasma samples were evaluated for relationships to the Modified Hammersmith Functional Motor Scale (MHFMS) in both LC/MS and Luminex immunoassay MAP platforms. There were 45+ analytes in common between the LC/MS and MAP platforms and the results were correlated well between them (R=0.65). Of the 9 analytes that were LC/MS hits that were represented in the MAPs, 6 of them reproduced as hits. The top combined hits from both platforms were selected on a basis of statistical strength and assay performance, and many of them have either restricted expression in bones, nervous system or muscle tissue or enriched expression in these tissues. B-C: New immunoassays were generated for the top 9 biomarkers identified by LC/MS analysis. These assays were developed and quality tested with SMA samples from the PNCR Natural History Study collection and analyzed against the Expanded HFMS (HFMSE). The plasma protein levels of these analytes correlated with the HFMSE with R-values that ranged from 0.66 to 0.87 and had differentiable levels across SMA types - with the exception of Tenascin XB. A reliable assay for CILP2 was not developed due to lack of usable reagents.

### Figure 1: Hit Generation Plan and

Representative New Analyte Relationship to SMA Function and Type



### **Results:**

Testing in the existing MAPs produced 72 new candidate marker hits. Another 8 markers hits identified separately in the BforSMA study were reproduced in the MAPs. Working assays for the top 9 BforSMA hits have been produced in singleplex and pilot multiplex formats, and a final panel of the top 35 combined hits will be tested with new SMA plasma samples to verify the candidate markers.

## Methods

### Data and Samples

The data herein was generated in an effort to identify a marker or panel of markers in plasma from a wide range of SMA patients that segregates with measures of clinical severity. Markers were identified as hits for their association with disease severity as determined by motor function or other functional outcome measures. Data was generated across three different discovery studies or campaigns. The first platform was a **LC/MS** iTRAQ analysis done by BG Medicine. The second and third were the **DiscoveryMAP** and **OncologyMAP** multiplexed immunoassay panels developed by Rules-Based Medicine. Samples used were plasma samples collected in the Biomarkers for SMA Study. This study was a multi-center, pilot study enrolling 130 subjects, age 2 to 12 years from 18 academic pediatric neuromuscular clinics. Each subject was seen for a single visit, during which an assessment of functional ability, pulmonary status and nutritional status was performed. No therapeutic intervention occurred.

Three groups of SMA patients and one cohort of control children was enrolled according to the classifications below:
Children with type I SMA (n=17).
Children with type II SMA (n=49).
Children with type III SMA (n=42).

Control children (n=22)

129 plasma samples were collected from the SMA patients and matched control subjects. These samples were used in ensuing LC/MS and MAP platform biomarker analyses.

Other samples from the Pediatric Neuromuscular Clinical Research Network (PNCR) SMA Natural History Study (NHS) from Columbia University, Boston Children's Hospital and Children's Hospital of Philadelphia were used for assay development. This study was a multisite, longitudinal prospective study enrolling 101 patients age 4 months to 45 years from three academic pediatric neuromuscular clinics. Subjects were seen at 0, 6, 12, 18, 24, 30 and 36 month visits, during which assessments using multiple motor scales and tests were made; pulmonary status, strength, nerve/muscle physiology and nutritional status assessments were also performed. No therapeutic Intervention occurred.

Three SMA groups from the PNCR NHS were enrolled according to the classifications below:
Subjects with type I SMA (n=27).
Subjects with type II SMA (n=40).
Subjects with type III SMA (n=34).

### **Statistical Analysis**

The LC/MS analyte data was analyzed using univariate and multivariate regression methods. Age and gender were controlled for in the analysis. Hits were identified by significant p-values whereby the lowest p-values were the strongest hits. The MAPs were analyzed using ANOVA, t-test, Fisher's Exact test, and Pearson's correlation and by multivariate regression analysis (linear, lasso, random forest). Analytes that had a high number of missing values (greater than 40% below limit of detection) were excluded from the analyses. Analytes whose values were driven by a few outliers generally fell out of the hitlist using these analyses. The false discovery rate (FDR) was controlled by the Benjamin Hochberg method and the FDR q-value cutoff was set at 0.10.

Further multivariate analyses were performed on both the LC/MS and MAP data to identify the best hits from all three discovery campaigns (Figure 1). The ability of top hits to predict SMA function scores is represented in Figure 2.

### LC/MS iTRAQ

Abundant proteins were depleted in order to facilitate a good dynamic range of protein measurements. In this project a dual affinity depletion strategy was implemented: in the first stage, 14 highly abundant proteins (serum albumin, IgG, fibrinogen, transferrin, IgA, IgM, haptoglobin,  $\alpha$ -2-macroglobulin,  $\alpha$ -1 acid glycoprotein,  $\alpha$ -1 antitrypsin, Apo A-I, Apo A-II, complement C3, and Apo B-100) were depleted by IgY antibody column. The remaining proteins were extracted from non proteinaceous components by reverse-phase chromatography. The proteins were reduced, alkylated (cysteine residues) and digested with trypsin. The resulting peptide pool was then labeled with the amine specific iTRAQ reagents. Eight samples labeled with eight different isotope-coded versions of the iTRAQ reagent were combined into eight-plex iTRAQ mixes and analyzed as a single sample using mass spectrometry. Each iTRAQ mix is analyzed by two dimensional LC-MS/MS. iTRAQ mixes are pre-fractionated by strong cation exchange into six fractions that are further separated by HPLC. The mass-to-charge ratios are the primary data used to determine whether individual analytes are "hits" (Table 1).

0.069	CARBONIC ANHYDRASE I	CA1
0.069	PROTEIN TYROSINE PHOSPHATASE, RECEPTOR TYPE, G	PTPRG
0.069	MYOGLOBIN	MB
0.069	NIDOGEN 1	NID1
0.069	TRIOSEPHOSPHATE ISOMERASE 1	TPI1
0.072	PLATELET FACTOR 4 (CHEMOKINE (CXC MOTIF) LIGAND 4)	PF4
0.077	PLASMA GLUTAMATE CARBOXYPEPTIDASE	PGCP
0.081	S100 CALCIUM BINDING PROTEIN A8 (CALGRANULIN A)	S100A8
0.081	GLYCERALDEHYDE3PHOSPHATE DEHYDROGENASE	GAPDH
0.081	CONTACTIN 4	CNTN4
0.081	SEX HORMONEBINDING GLOBULIN	SHBG
0.081	TRANSGELIN 2	TAGLN2
0.081	AFAMIN	AFM
0.081	NUCLEOSIDE PHOSPHORYLASE	NP
0.081	HAPTOGLOBIN	HP
0.081	DYSTROGLYCAN 1 (DYSTROPHINASSOCIATED GLYCOPROTEIN 1)	DAG1
0.082	PROTEIN C RECEPTOR, ENDOTHELIAL (EPCR)	PROCR
0.082	ACTININ, ALPHA 1	ACTN1
0.082	COLONY STIMULATING FACTOR 1 RECEPTOR, FORMERLY MCDONOUGH FELINE SARCOMA VIRAL (VFMS) ONCOGENE HOMOLOG	CSF1R
0.082	PEROXIREDOXIN 2	PRDX2
0.082	GLUTATHIONE SYNTHETASE	GSS
0.082	S100 CALCIUM BINDING PROTEIN A9 (CALGRANULIN B)	S100A9
0.082	THIOREDOXIN	TXN
0.082	SUPEROXIDE DISMUTASE 1, SOLUBLE (AMYOTROPHIC LATERAL SCLEROSIS 1 (ADULT))	SOD1
0.083	PEROXIREDOXIN 6	PRDX6
0.090	SERPIN PEPTIDASE INHIBITOR, CLADE D (HEPARIN COFACTOR), MEMBER 1	SERPIND1
0.090	MULTIMERIN 2	MMRN2
0.090	CHONDROADHERIN	CHAD
0.096	CALCIUM CHANNEL, VOLTAGE DEPENDENT, ALPHA 2/DELTA SUBUNIT 1	CACNA2D1
0.109	OROSOMUCOID 1	ORM1
0.131	AMINE OXIDASE, COPPER CONTAINING 3	AOC3

0.067

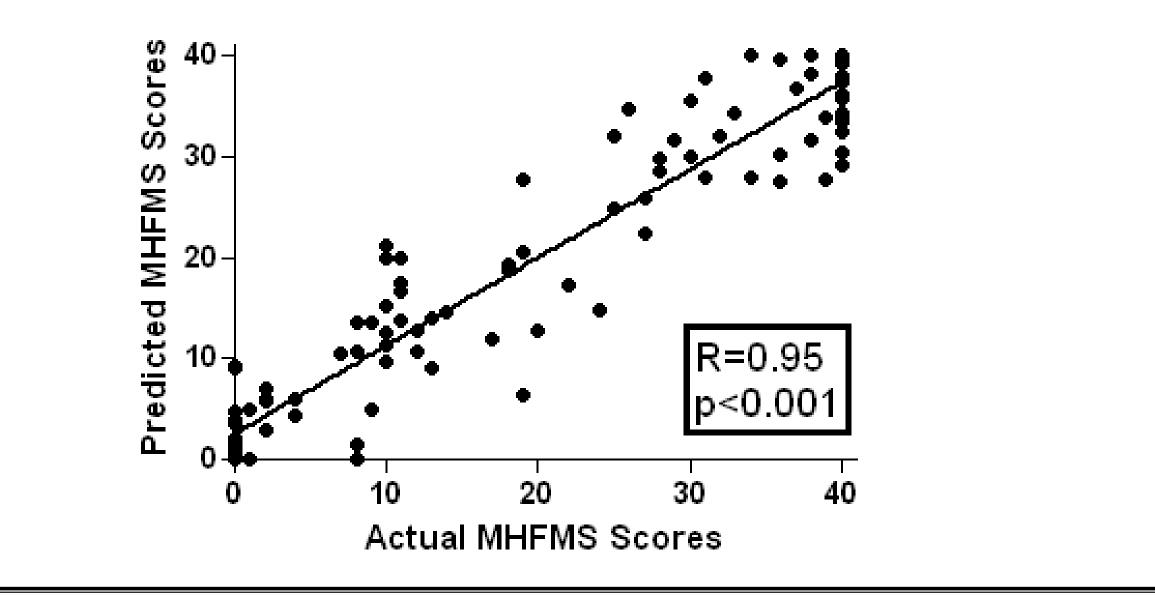
VANIN 1

### Table 2: DiscoveryMAP Plasma Protein Hitlist

P-VALU	DESCRIPTION	PROTEIN
<0.001	Myoglobin	MB
<0.001	Osteopontin	SPP1
<0.001	AXL Receptor Tyrosine Kinase	AXL
<0.001	Serum Amyloid P Component	APSC
<0.001	C Reactive Protein	CRP
<0.001	Macrophage Derived Chemokine	MDC
<0.001	Thrombomodulin	ТМ
<0.001	Calcitonin	CALCA
<0.001	Leptin	LEP
<0.001	Brain Naturipetic Peptide	BNP
<0.001	Matrix Metalloproteinase 2	MMP2
<0.001	Creatine Kinase MB	СКМ
	Angiotensin Converting Enzyme	ACE
<0.001	Fatty Acid Binding Protein heart	FAPB4
< 0.001	CD40 Ligand	CD40
< 0.001	Macrophage Migration Inhibitory Factor	MIF
<0.001		ANGPT2
< 0.001	Angiopoietin 2 Fetuin A	FETUA
0.001		CHFH
0.001	Complement Factor H	
0.001	Interleukin 8	IL8 C3
0.001	Complement C3	PPP
0.001	Pancreatic Polypeptide	
0.002	Vascular Endothelial Growth Factor	FLT1
0.002	Transferrin	TF
0.002	Placenta Growth Factor	PLGF
0.002	Epidermal Growth Factor	EGF
0.002	Glutathione S Transferase alpha	GSTA1
0.003	Superoxide Dismutase 1	SOD1
0.003	Vascular Cell Adhesion Molecule 1	VCAM1
0.004	Plasminogen Activator Inhibitor 1	PAI1
0.004	Macrophage Colony Stimulating Factor	M-CSF
0.004	S100 Protein A12	S100A12
	Vitronectin	VTN
0.004	Fas Ligand	FASLG
0.006	Alpha 1 Microglobulin	A1M
0.007	Serum Glutamic Oxaloacetic Transaminase	SOT
0.009	Alpha 1 Antichymotrypsin	ACCT
0.01	Macrophage Inflammatory Protein 1 beta	MIP1b
0.011	Sortilin	SORT1
0.013	Thyroxine Binding Globulin	TBG
0.014	Apolipoprotein A I	APOA1
0.015	Myeloperoxidase	MPO
0.016	Beta 2 Microglobulin	B2M
0.016	Erythropoietin	EPO
0.017	Matrix Metalloproteinase 10	MMP10
0.02	Vitamin K Dependent Protein S	PROS1
0.023		MMP7
0.025	Matrix Metalloproteinase 7	RAGE
0.029	Receptor for advanced glycosylation end products Interleukin 18	
0.033		IL18
0.034	Chemokine C-C Motif Ligand 11	CCL11
0.035	ImmunoglobulinA	IgG
0.041	Proinsulin C Peptide	C peptide
0.041	Alpha 2 Macroglobulin	A2M
0.042	Platelet Derived Growth Factor	PDGF BB
0.047	Chemokine C-C Motif Ligand 16	CCL16
0.049	Interleukin 1 alpha	IL1a
0.049	Apolipoprotein A IV	APOA4
0.05	MATRIX METALLOPROTEIN 9	MMP9

Preliminary Predictive Power of a Subset of SMA Plasma Protein Analytes A group of 25 MAP plasma protein analytes were used to generate predicted MHFMS scores for the BforSMA study samples from SMA patients. The subpanel analytes were able to account for up to 95% of the variance in the MHFMS scores.

### Figure 2: Correlation between Actual MHFMS Scores and Scores Predicted by a Panel of 25 Protein Hits



### Immunoassay Multi-Analyte Profile (MAP)

Multiplexing is accomplished by assigning each analyte-specific assay a microsphere set labeled with a unique fluorescence signature. To attain distinct microsphere signatures, two fluorescent dyes, red and far red, are mixed in various combinations using different intensity levels of each dye. Each set of microspheres is encoded with a fluorescent signature by impregnating the microspheres with a unique dye combination. After the encoding process, an assay-specific capture reagent is conjugated covalently to each unique set of microspheres, creating an ELISA-like assay on each bead surface.

After optimizing the parameters of each assay separately, Multi-Analyte Profiles (MAPs) are performed by mixing up to 100 different sets of the microspheres in a single well of a 96- or 384-format microtiter plate. A small sample volume of plasma (10uL – 20uL) is added to the well and allowed to react with the microspheres. The assay-specific capture reagent on each individual microsphere binds the analyte of interest. A cocktail of assay specific, biotinylated detecting reagents (e.g., antigens, antibodies, ligands, etc.), is reacted with the microsphere mixture, followed by a streptavidin-labeled fluorescent "reporter" molecule. Finally, the multiplex is washed to remove unbound detecting reagents. After washing, the mixture of microspheres is analyzed using the Luminex 100<sup>™</sup> instrument. Similar to a flow cytometer, the instrument uses hydrodynamic focusing to pass the microspheres in single file through two laser beams. As each individual microsphere passes through the excitation beams, it is analyzed for size, encoded fluorescence signature and the amount of fluorescence generated in proportion to the analyte. As each microsphere is encoded with a unique signature, the classification identifies the analyte being measured on that individual microsphere. As the microsphere passes through a green diode-pumped solid state laser (532 nm), a fluorescence "reporter" signal (580 nm) is generated in proportion to the analyte concentration. Analyte concentrations from the DiscoveryMAP and OncologyMAP panels were analyzed to identify hit proteins (Table 2, 3).

#### SMA MAP Panel

The top hits were identified and selected for their statistical value and assay performance for use in a new SMA MAP panel with both LC/MS and DiscoveryMAP and OncologyMAP analytes. New immunoassays were created for the top 9 LC/MS 9 analyte hits: Tenascin XB, Cartilage Intermediate Layer Protein 2, CD93, Cartilage Oligomeric Protein, Lumican, Cadherin13, Dipeptidyl peptidase 4, Peptidase D, and Thrombospondin-4 (THB4 example in Figure 2).

# **Discussion and Next Steps**

- Hits from the LC/MS and MAP biomarker discovery studies have been combined into a new custom multiplexed immunoassay panel for SMA
- The SMA panel is being tested with other SMA sample collections to verify the initial BforSMA results
  - Results will be available by end of July
  - Analysis will include regression against several other SMA motor scales (e.g. GMFM, HFMSE) and outcome measures (e.g. FVC, CMAP/MUNE)
- This SMA panel will be available in August 2011 for further community testing as a prognostic and possibly pharmacodynamic biomarker tool
  - A streamlined version of the panel will be available in Fall 2011
- Please see BforSMA database poster #26B

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