

Non Receptor Tyrosine Kinases Activated upon B or T cell receptor engagement

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**Activated upon BCR
engagement**

SRC Family
Lyn
Blk

SYK Family
Syk

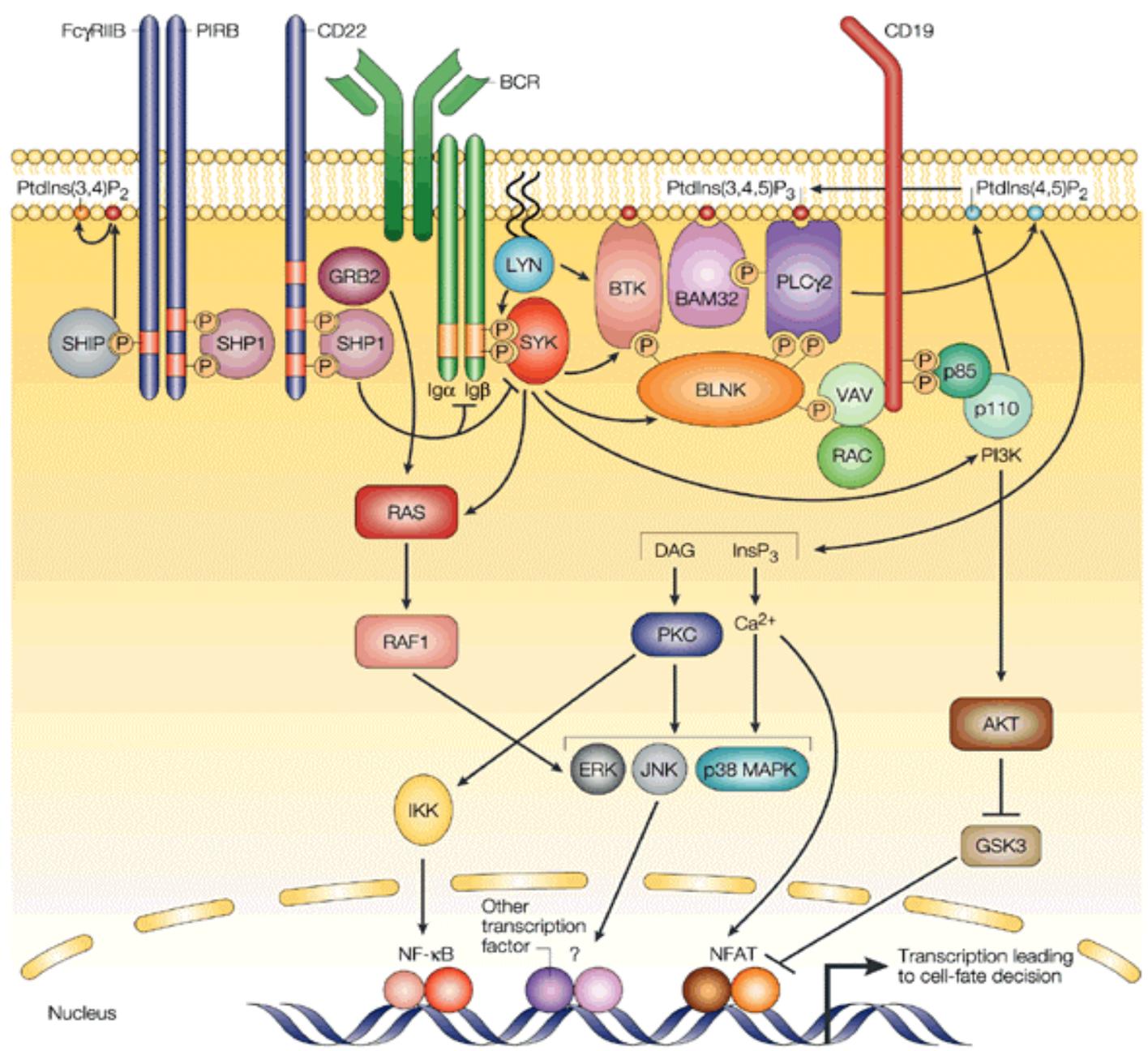
TEC family
Btk

**Activated upon TCR
engagement**

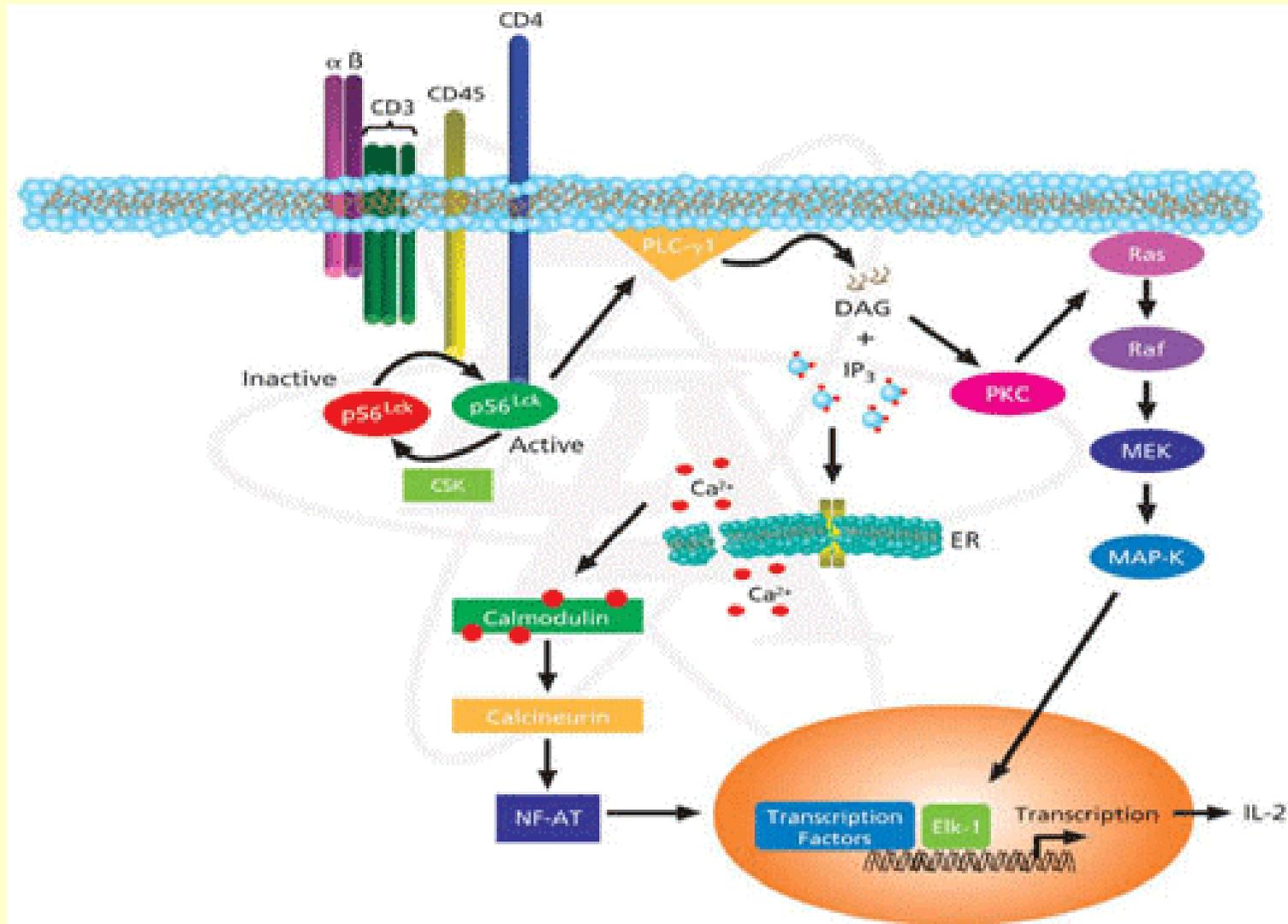
SRC Family
Lck
Fyn

SYK Family
Zap-70

CSK family
Csk



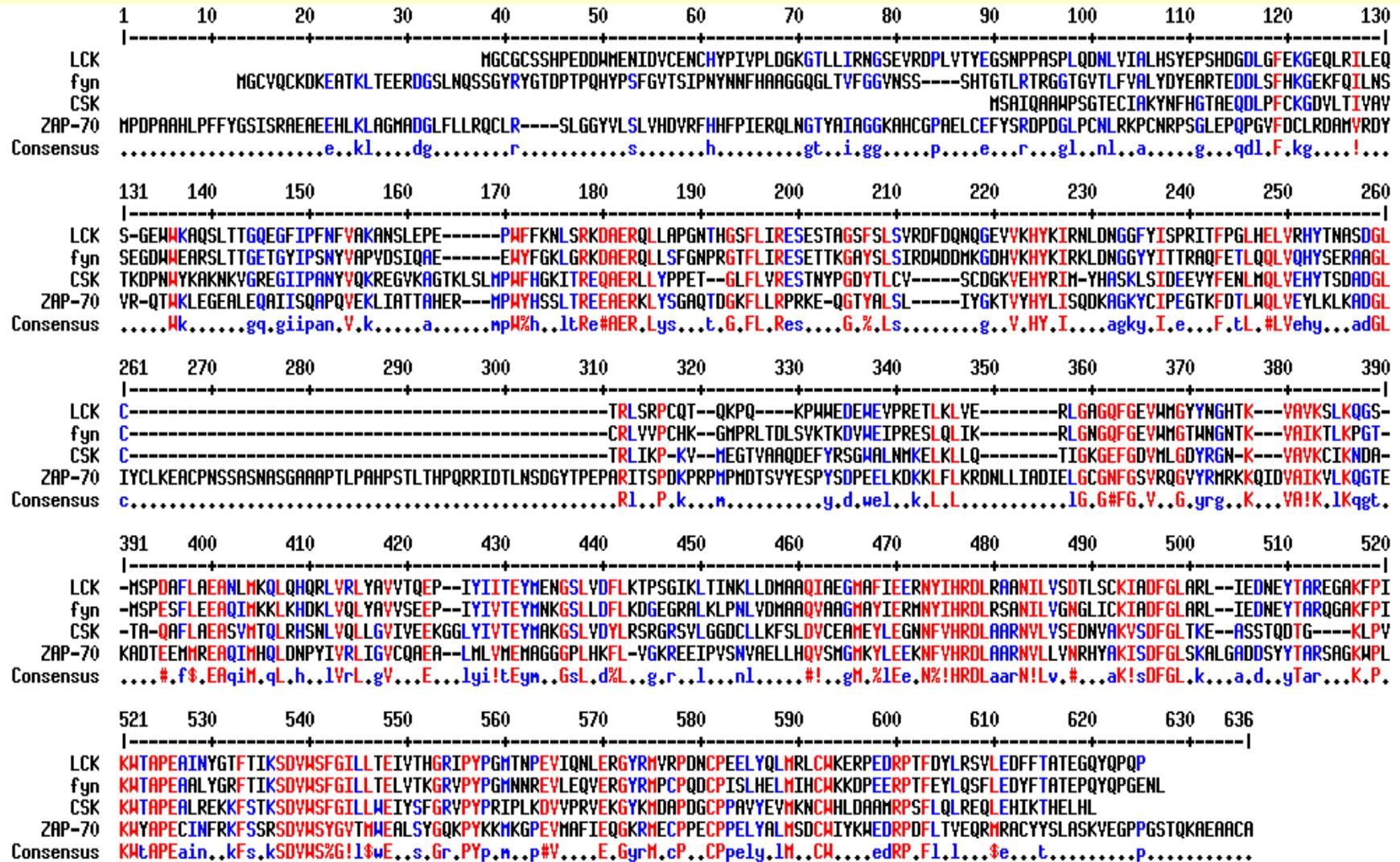
T Cell Receptor (TCR) Signaling



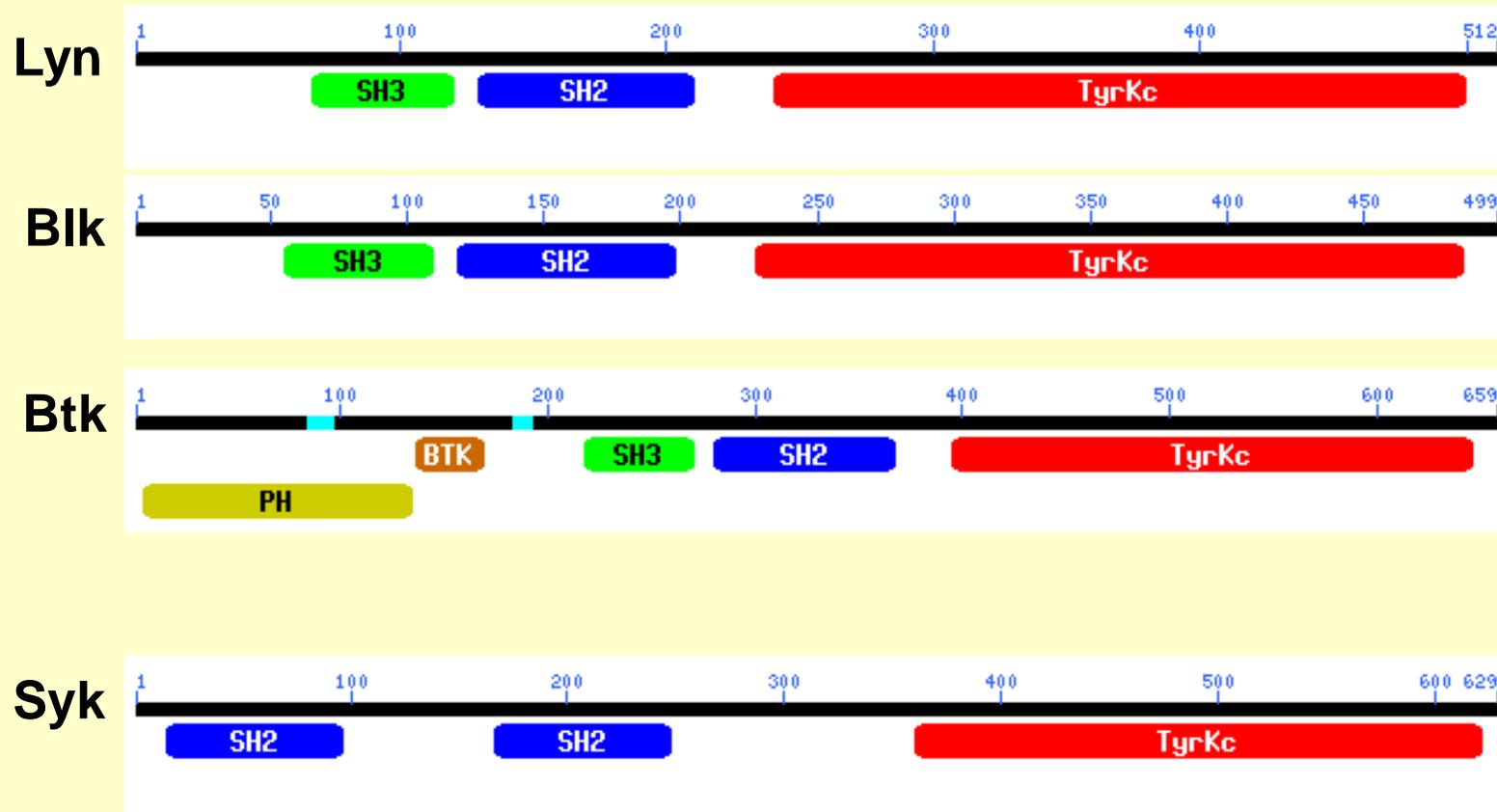
	1	10	20	30	40	50	60	70	80	90	100	110	120	130
Lyn	-----													
BLK														
BTK	MAAVILESIFLKRSSQKKKTSPLNFKKRLFLLLVHKLSSYYEYDFERGRGSKKGSIDVEKITCVETVIPEKNPPPERQIPRRGEESSEMEQISIIERFPYPFQVYVDEGPLYVYFSPTEELRKRNIHQLN													
SYK	MAGSAVDSANHLTYFFGNITRREAREYDLVQGGMTDGLYLLRQSRNLYGGFALSVAHNRKAHHYTIERLNGTYAI---SGGRAHASPADLCH---YHSQEPD													
Consensusv.....y.f.....r.....v.....i.....g.....sp.....q...													
	131	140	150	160	170	180	190	200	210	220	230	240	250	260
Lyn	-----													
BLK	MGCICKRKRKDNLNDDDEVDSKTQPVYRNTDRTIYVRDPTSNKQQRVPVPEFHLLPGQRFQTKDPEEQGDIYVVALYPYDGFHPDDL SFKKGEKMKVLEEHG-EHWKAKSLSSK													
BTK	MGLLSSKRQVS---EKKGMSPVK----IRTQDKAPPPLPPLVYFNHLAPPSPNQ--DPDEEERFVVALFDYAAVNDRLQVLKGEKLQVLRSTG-DHWLARSLVYG													
SYK	VIRCNLDLVQYHPCFHDIGQYLCCSQTAKNANGCQILENRNGSLKPGSSHRKTKKPLPPTPEEDQILKPLPEPTAAPTISTTELKVVVALYDYNPMNANDLQRKGEYFII EESNLPWRRARD-KNG													
Consensus	...c...l.....g.....n.....k...n.....i...qkp...kl.....k...P.....e.#...v!al..y..f..rdl...kge.l..L.e....uwra....ktg													
	261	270	280	290	300	310	320	330	340	350	360	370	380	390
Lyn	-----													
BLK	REGFIPSNVYAKYN-TLETEEWFKDIRKDAERQLLAPGNSAGAFIIRESETIKGSFSLSVRDYDPMHGDVIKHYKIRSLDNGGYYISPRITFPICISDIKHYKQSDGLCRRLKACISPKPQKP---													
BTK	REGYVPSNFVAPVE-TLEVEKWFRTISRKDAERQLLAPNKAQSFIIRESNKGAFLSVKDIITQ-GEVVKHYKIRSLDNGGYYISPRITFPITLQALVQHYSKKG DGLCQKLTLPVNLAPKNL---													
SYK	QEGYIPSNYITEAEDSIEHYEYSKHMTRSQAERQLLKQEGKEGGFIVGDSSKAGKYTVSVFAKSTGEPQG-VIRHYVVCSTPQSQYYLAEKHLFSTIPELINYHQHNSAGLISRLKYPVSKQKNAPSTA													
Consensus	.eg..psn.....E.y.u.....R..ae..L..p..k.Ga..g..s..nk..vs.s...i...g.v..hy...s.p...yy..p..tfs..p.....dgl.qrl.lp.....p...													
	391	400	410	420	430	440	450	460	470	480	490	500	510	520
Lyn	-----													
BLK	-MDKDAWEI--PRESIKLV-KKLGAGQFGEVWNGYYNNST---KVAVKTLKLGTHSV---QAFLEEARLHKTLQHDKLVRLYAVVTKKEPIYIITEFMAKGSLLDFLKSDEGGKVLPLKIDFSAQIAREG													
BTK	-MAQDEWEI--PRQSLKLV-RKLGSGQFGEVWNGYYKNM---KVAIKTLKEGTMSV---EAFLEEARVHKTLQHERLVRLYAVVTR-PIYIVTEYMARGLLDFLKTDEGSRLSLPRIDMSAQVAREG													
SYK	GLGYGSAWEI--DPKDLTFL-KELGTFQFVYKYGKRRGQY---DVAIKMIREGSHSE---DEFIEEARVHMLSHKLVQLYGVCTKQRFIITEYMARGLLNYLR-ENRHRFQTQQLLEHCKDVCER													
ConsensuswE!..dr..ltl...eLGS#FG.Vk.Gyy.....VAIK.lk.g.nsp...#efl.EAnvM..L.h..lvr\$gg!ct.#.pi.i!tE.na.G.Ll.%L.....li#...#!.eg													
	521	530	540	550	560	570	580	590	600	610	620	630	640	650
Lyn	-----													
BLK	MAYIERKNYIHRDLRAANLVSESLMCKIADFGLARIIEDNE--YTAREGAKFPIKHTAPEAIFGCFITIKSDVMSFGILLYEIVTYGKIPYGRTNADVMSALSQGYRMPRMENCPDELY-DIMKMCWK													
BTK	MAYIERMNSIHRDLRAANLVSETLCCKIADFGLARII-DSE--YTAQEGAKFPIKHTAPEAIFGVFTIKADVMSFGVLLMEIVTYGRVPYPGMSNPEVIRSLHEGYRMPCPETCPPELYNDIITECWR													
SYK	MEYLESKQFLHRDLAARNCLVNDQGVVKVSDFGLSRYVLDE--YTSVSGSKFPVRSPPPEVLVMSKFSKSDIHAFGVLMHEIYSLGKMPYERFTNSEARAEHIAQGLRLYRPHLASERVY-TIMYSCWH													
Consensus	M..YIE..#f..HRDLaARnLv...q...K!sDFGLsr...dde...Ytaq.g.KfP!k.a.pE.in%.kFssKsD!HsFG!L\$wEi.syg..PY.gn.ns#v...le.G.R\$.cp...cp.e.Y.din...CH.													
	651	660	670	681										
Lyn	-----													
BLK	EKAERPTFDYLQSVLDDFYTATEGQYQQP													
BTK	GRPEERPTFEFLQSVLEDFYTATEGQYELQP													
SYK	EKADERPSFKILLSNILDVNDDES													
Consensus	...#RP.F..l.s.l.#.y.....													

	1	10	20	30	40	50	60	70	80	90	100	110	120	130
Lyn	MGCISKRKONLNDDVEVSKTQPVYRNTDRTIYVRDPTSNKQQRVPVEFHLLPGQRFQTKDPEEQGDIYVALYPYDGFHPDLSFKKGEKMKVLEEHGEHWKAKSLSSKREGFIPSNYVAKVNTLETEEWF													
BLK	MGLLSKRQVS---EKKGWSPVK----IRTQDKAPPPLPLVVFNHLAPPSPNQ--DPDEEERFVVALFDYAAVNDRLQVLKGEKLQVLRSTGDWHLARSLVTGREGYVPSNFVAPVETLEVEKWF													
Consensus	MGCiSKRQdn....EkdkgtqPv.....IrrtrDkapnkqqrLVpenHLaPgqrnQ..DP#E#eriVVAL%dyAafndrDLqfLKGEK\$qVLRhg#WHLArSLssgREG%!PSN%VAKV#TLEtEeWF													
	131	140	150	160	170	180	190	200	210	220	230	240	250	260
Lyn	FKDITRKDAERQLLAPGNSAGAFIIRESETIKGSFSLSVRDYDPMHGDVVKHYKIRSLDNGGYYISPRITFPICISDMIKHYQKQSDGLCRRLEKACISPKPQKPDWDAWEIPRESIKLYKKLGAQQFGE													
BLK	FRTISRKDAERQLLAPMNAKGSFLIRESESNKGFSLSVKIDITTQ-GEVVKHYKIRSLDNGGYYISPRITFPTLQALVQHYSKKGDLGCQKLTLPVNLAPKNLWAQDEWEIPRQSLKLYRKLGSQQFGE													
Consensus	FrdIsRKDAERQLLAPgnkAGaFLIRESEsnKGaFSLSVrDidpq.G#V!KHYKIRSLDNGGYYISPRITFPciqa\$!qHYqKqgDGLCrrLelaC!nlaPqnIWAQDAWEIPR#SiKLYrKLGAQQFGE													
	261	270	280	290	300	310	320	330	340	350	360	370	380	390
Lyn	VMGYYNNSTKVAVKTLKLGTHSVQAFLEEARLIMKTLQHQKLVRLYAVVTKEEPIYIITEFMAKGSLLDFLKSDEGGKVLPLKLIIDFSAQIAEGHAYIERKNYIHRDLRAANVLYSESLMCKIADFLGLAR													
BLK	VMGYYKNMVKVAIKTLKEGTMSPEAFLEEARVMKTLQHERLVRLYAVVTRE-PIYIVTEYMARGCLLDFLKTDEGSRLSLPRLIDMSAQVAREGHAYIERMNSIHRDLRAANILVSETLCKIADFLGLAR													
Consensus	VMGYYnNmKVAV!KTLKeGTMSp#AFLeEARLIMKTLQH#rLVRLYAVVTRE.PIYI!TE%MARGcLLDFLKSDEGgrlLPrLIDnSAQ!AREGHAYIERknsIHRDLRAAN!LYSESLcCKIADFLGLAR													
	391	400	410	420	430	440	450	460	470	480	490	500	510	513
Lyn	IIEDNEYTAREGAKFPIKHTAPEAInFGcFTIKSDVMSFGILLYEIVTYGKIPYPGRtNADVMSALSGYRMPRMENCpDELY-DIMKMCWKEKAERPTFDYLSVLDFFYTATEGQYQQP													
BLK	II-DSEYTAQEGAKFPIKHTAPEAInHFGVFTIKADVMSFGVLLMEIVTYGRVYPYpGMSNPEVIRSLHGYRMPCPETCPPELYNDIITECHRGPRPEERPTFEFLQSVLEDFYTATEGQYELQP													
Consensus	II.DnEYTArEGAKFPIKHTAPEAInFGcFTIKaDVMSFG!LLnEIVTYGr!PYpGrSNa#ViraLeqGYRMPRmEncpDELY.DIikeCHreraERPTF#%LQSVL#DFYTATEGQY#qQP													

Sequence Alignment of Non-Receptor Protein Tyrosine Kinases (NRPTK) Associated with Proximal T Cell Signalling



Similarities and differences in structural domains of non_receptor TK's Expressed in B-lymphocytes



Structural Domains of NR-PTK Associated with Proximal T Cell Signalling (BLAST)

LCK



FYN

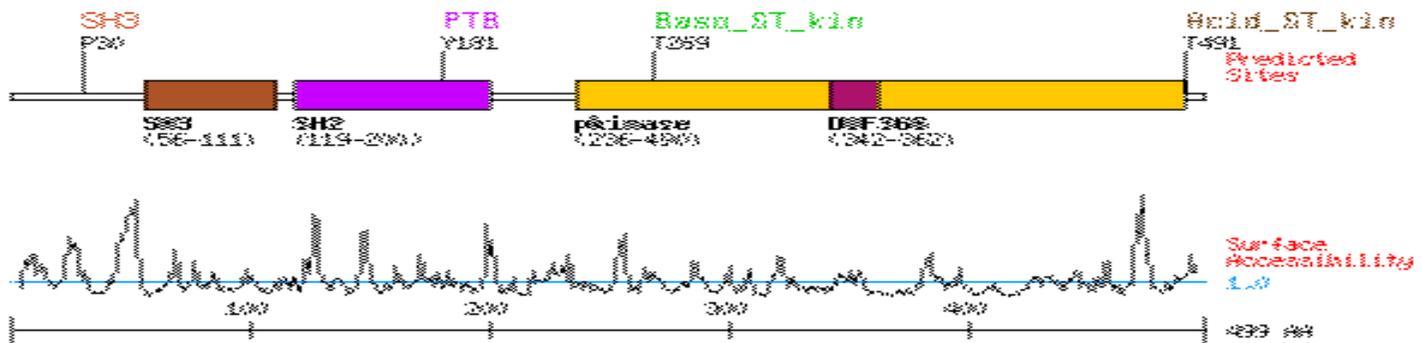
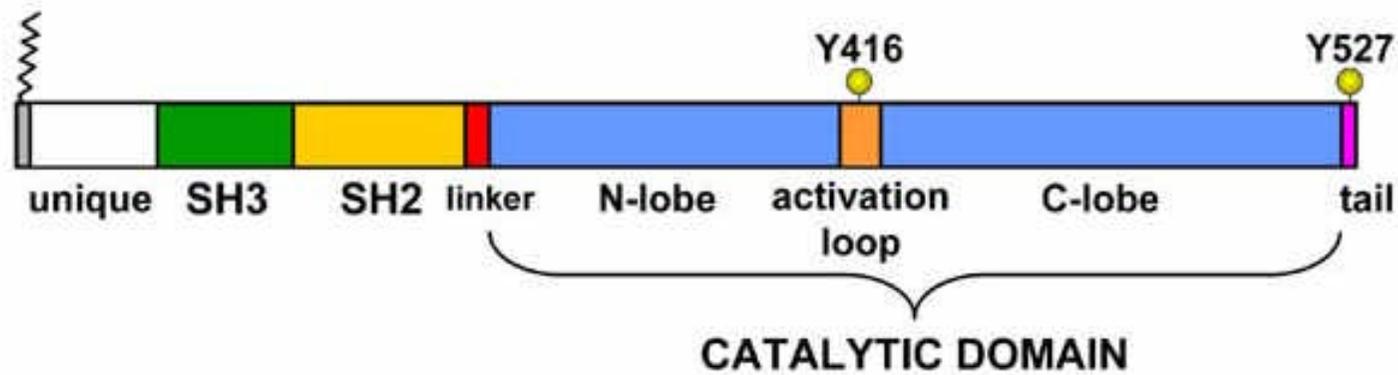


ZAP-70

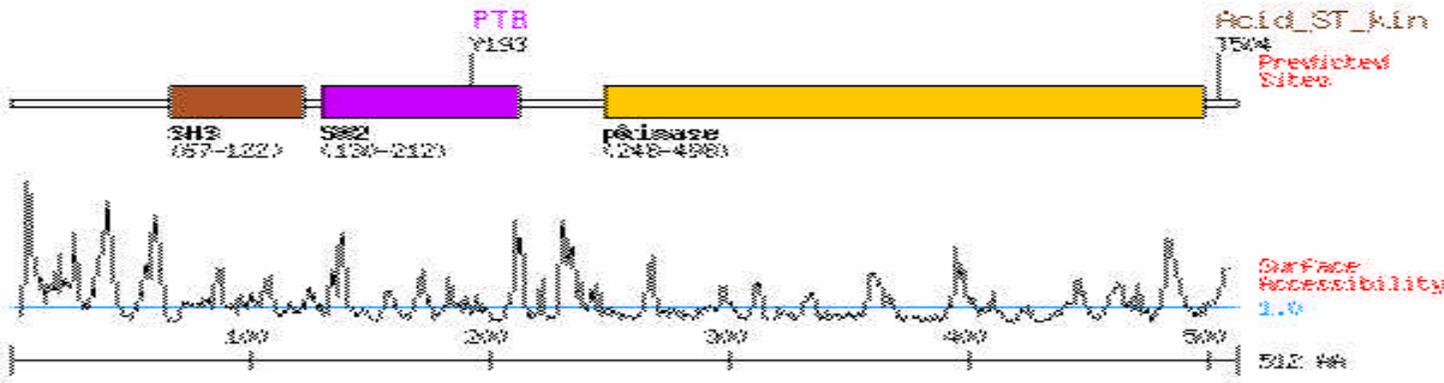


CSK

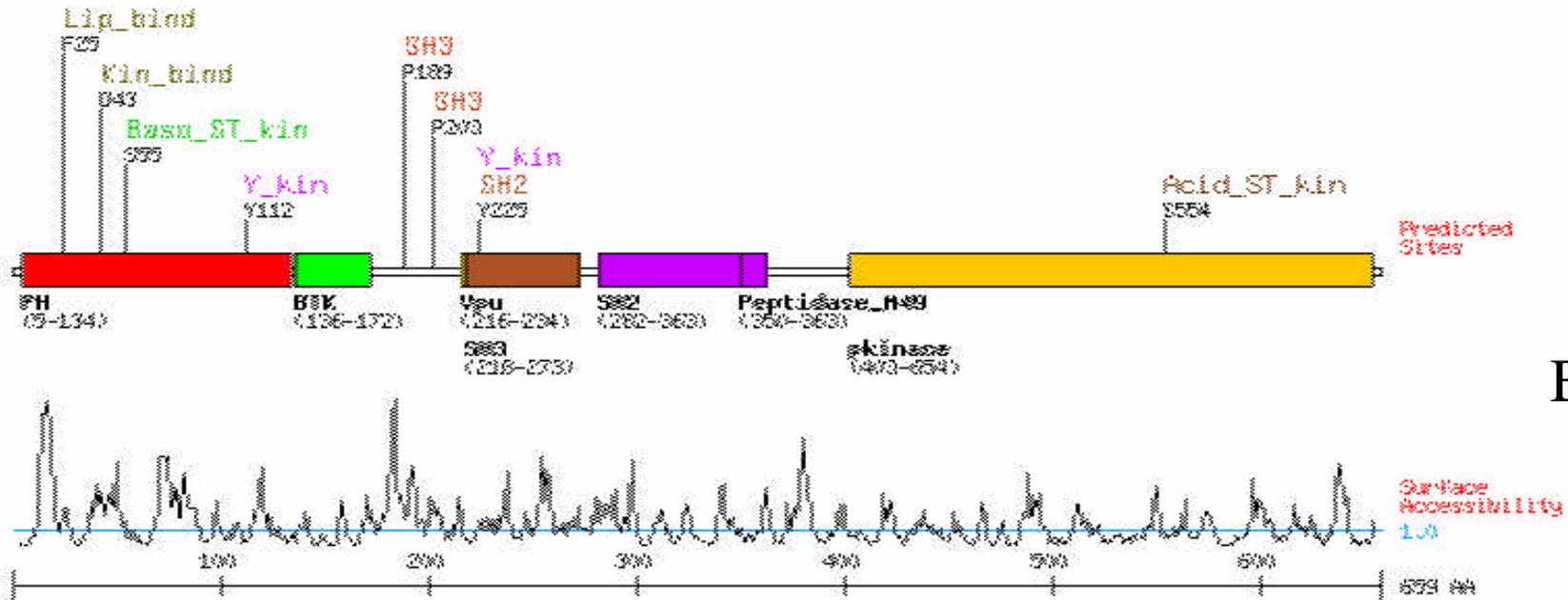
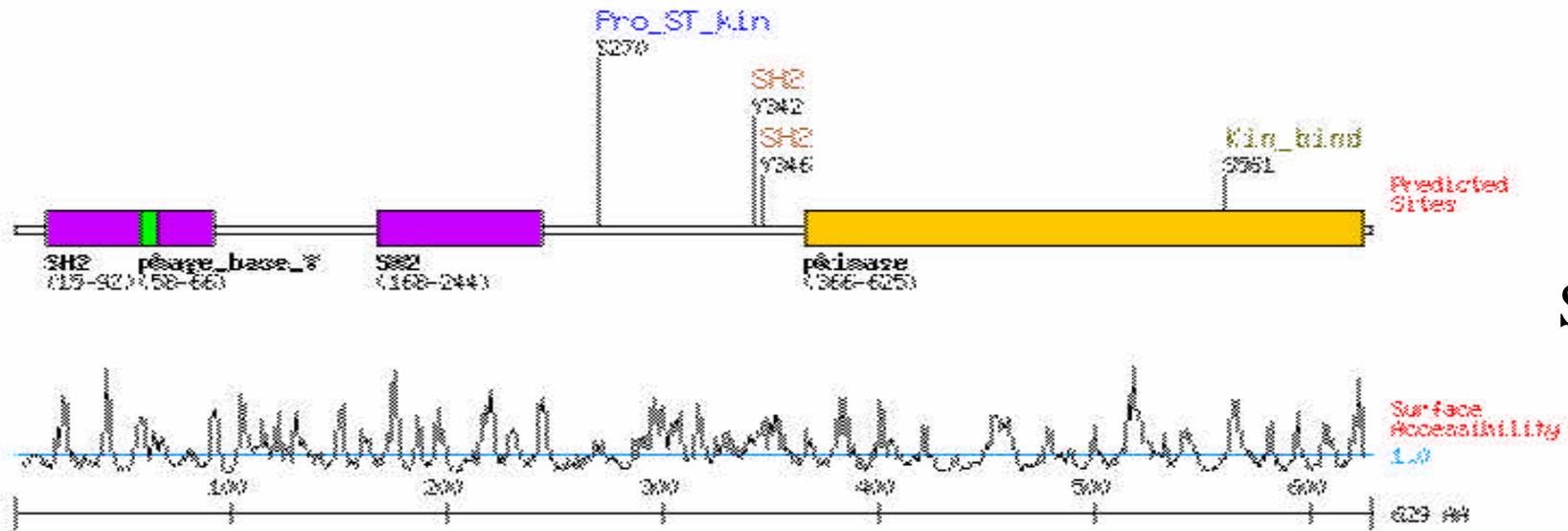




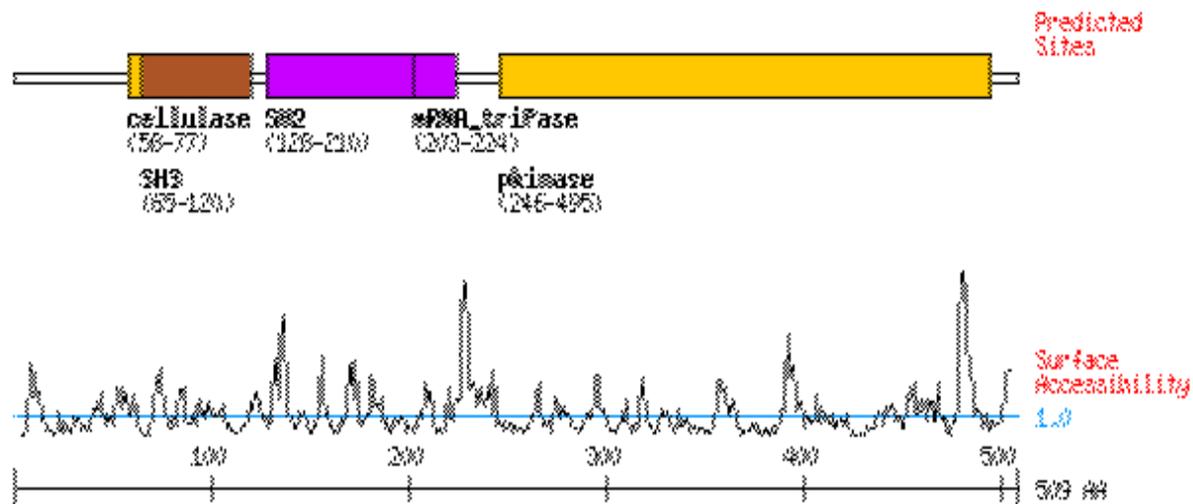
BLK



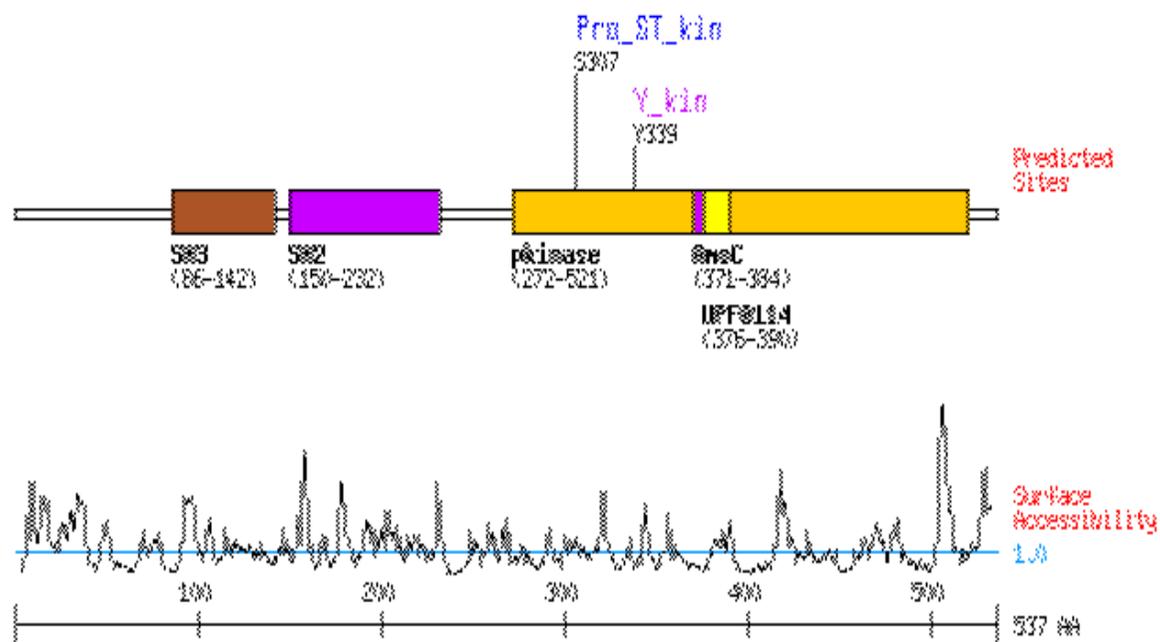
LYN



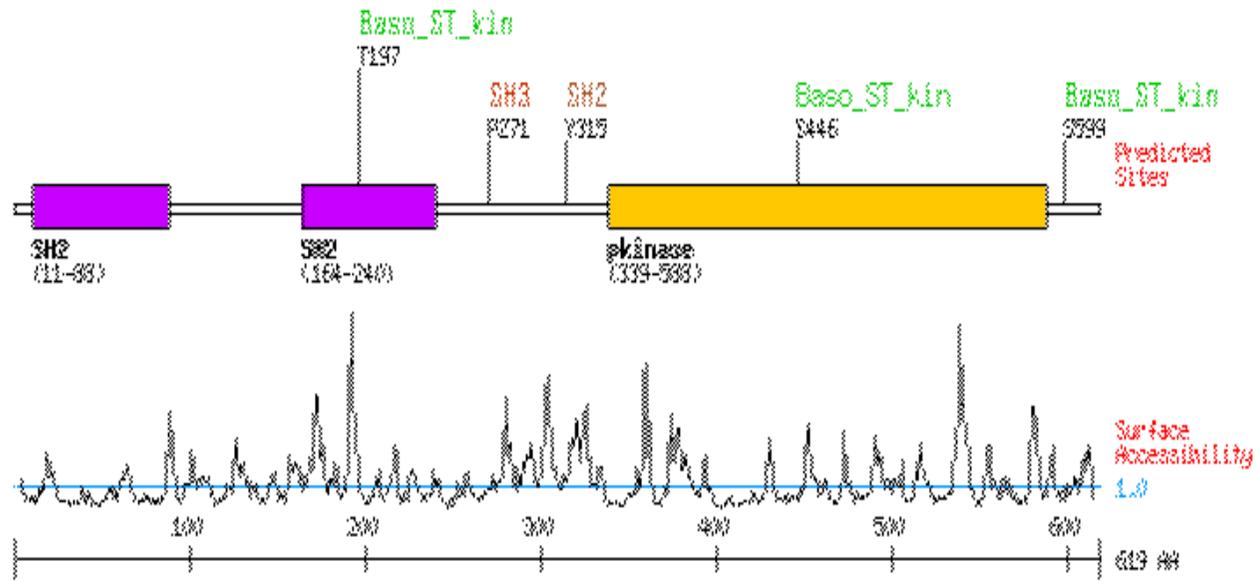
LCK



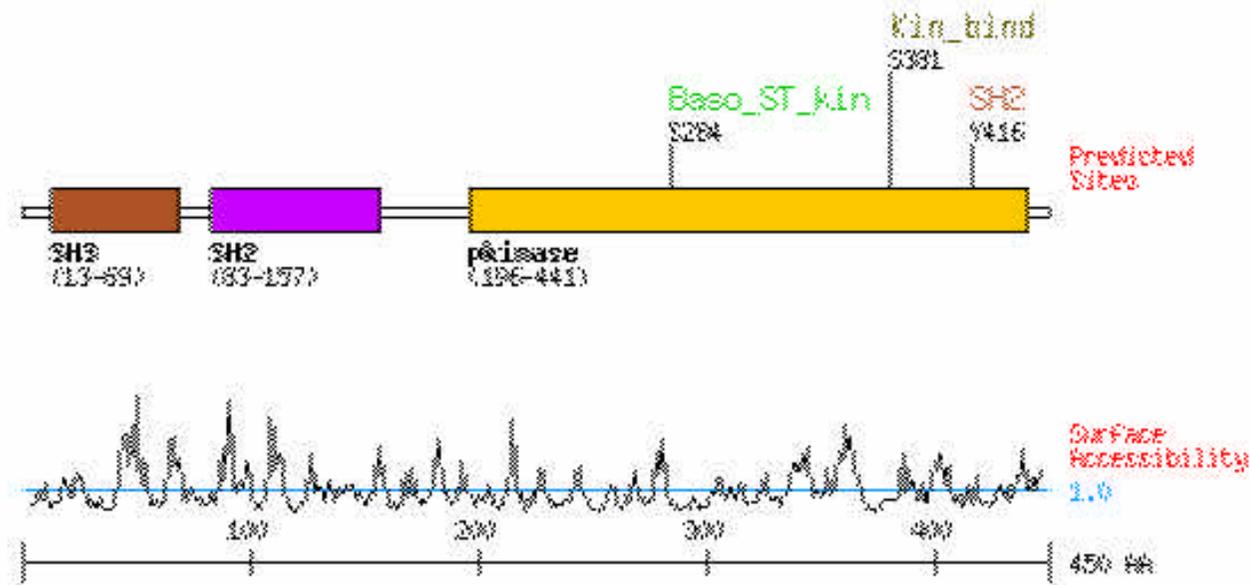
FYN



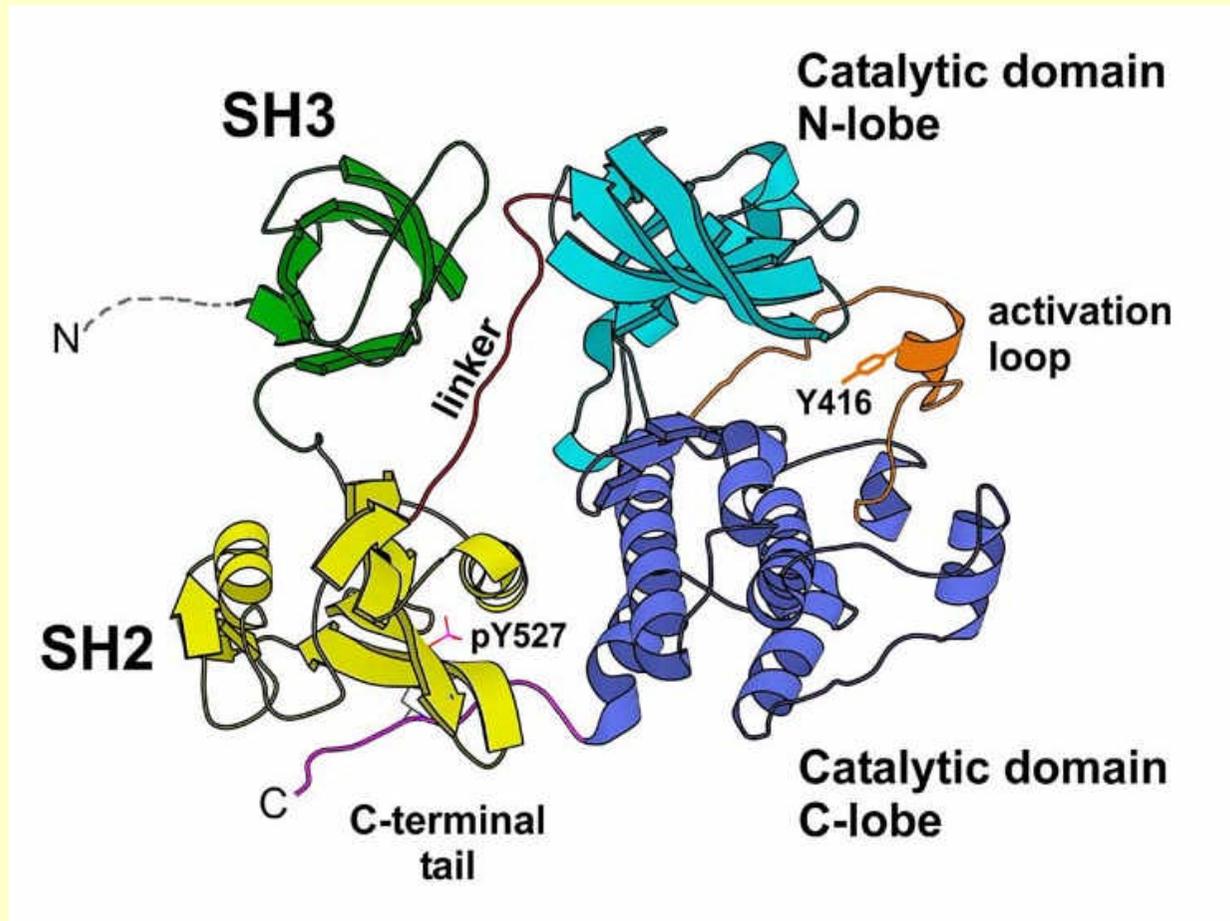
ZAP-70



CSK



Src Family



Myristoylation and phosphorylation sites in non-receptor protein tyrosine kinases expressed in B-lymphocytes

PTK	Myristoylation		Phosphorylation	
	Position	Sequence	Position	Sequence
Lyn	2-7	GCikSK	25 - 32	Rnt.Drti Y
			186 - 193	Rsl.Dngg Y
			390 - 397	RiieDne Y
			514 - 520	
Syk	32 - 37	GMtdGL	170 - 178	ReeaErkl Y
			190 - 198	RprkEqgt Y
			240 - 248	KlkaDgli Y
Blk	2-7	GLIsSK	174 - 181	Rsl.Dngg Y
			377 - 383	Rii.Dse. Y
			440 - 446	Rsl.Ehg. Y
Btk	50 - 55	GSkkGS	503 - 511	KdvcEame Y
			544 - 551	RyvIDde Y

T Cells

N-myristoylation site

Tyrosine kinase phosphorylation site

LCK

2 - 7 GCgcSS

387 - 394 RlieDne

FYN

2 - 7 GCgcSS

206 - 213 Rkl.DnggY
413 - 420 RlieDne.Y

ZAP-70

N/A

170 - 178 ReeaErklY
190 - 198 RprkEqgtY
240 - 248 KlkaDgliY

CSK

N/A

89 - 97 ReqaErllY
137 - 145 KlSiDeevY

Mapping

BTK

By RFLP studies in 11 families, they showed that XLA is linked to 2 markers, DXS3 and DXS17, both localized in region Xq21.3-q22 (lod = 3.65 at theta = 0.04 and lod = 2.17 at theta = 0.0, respectively). In a single 8-generation Dutch kindred, [Mensink et al. \(1986\)](#) found a maximum lod score of 3.30 at a recombination fraction of 0.06 for linkage of XLA and marker p19-2 (DXS3) By RFLP studies in 11 families, they showed that XLA is linked to 2 markers, DXS3 and DXS17, both localized in region Xq21.3-q22 (lod = 3.65 at theta = 0.04 and lod = 2.17 at theta = 0.0, respectively). In a single 8-generation Dutch kindred, [Mensink et al. \(1986\)](#) found a maximum lod score of 3.30 at a recombination fraction of 0.06 for linkage of XLA and marker p19-2 (DXS3)

SYK

[Ku et al. \(1994\)](#) used isotopic in situ hybridization to demonstrate that the SYK gene is located on 9q22 in the human and chromosome 13 in the mouse

LYN

By hybridization analysis of DNA from sorted chromosomes, [Yamanashi et al. \(1987\)](#) mapped the LYN gene to chromosome 8q13-qter.

BLK

By a study of intersubspecies backcrosses, [Kozak et al. \(1991\)](#) mapped the Blk gene to mouse chromosome 14. [Islam et al. \(1995\)](#) reported the molecular cloning of the human BLK gene and its expression. By fluorescence in situ hybridization and somatic cell hybrid analysis, they mapped BLK to 8p23-p22. This region is homologous to the region of chromosome 14 carrying the mouse blk locus.

Mouse Models

LYN

[Hibbs et al. \(1995\)](#) demonstrated that mice homozygous for a disruption of the Lyn locus display abnormalities associated with the B-lymphocyte lineage and in mast cell function. Lyn-deficient mice show IgM hyperglobulinemia. Immune responses to T-independent and T-dependent antigens were affected. The deficient mice failed to mediate an allergic response to IgE cross-linking, indicating that activation of Lyn plays an indispensable role in signaling by the high-affinity IgE receptor (FCER). Homozygous deficient mice had circulating autoreactive antibodies, and many showed severe glomerulonephritis caused by the deposition of IgG immune complexes in the kidney, a pathology reminiscent of systemic lupus erythematosus. [Hibbs et al. \(1995\)](#) stated that, collectively, these results implicated LYN as having an indispensable role in immunoglobulin-mediated signaling, particularly in establishing B cell tolerance.

BTK

Presumably the X-linked B lymphocyte defect of mice, studied by [Marshall-Clarke et al. \(1979\)](#), is homologous. This defect is characteristic of the CBA-N strain of mice ([Scher et al., 1975](#)). Defective mice lack the subpopulation of B lymphocytes responsive to certain T-independent antigens of which trinitrophenylated (TNP)-Ficoll is the prototype. Their responses to T-dependent antigens may also be impaired and they are unable to respond to the hapten phosphorylcholine (PC). They lack those B cells that form colonies when cultured in vitro.

SYK

[Colucci et al. \(2002\)](#) showed that mice lacking Syk have a failure of B-cell development.

BLK

[Dymecki et al. \(1990\)](#) reported the specific expression of a novel tyrosine kinase gene, Blk, in B lymphocytes of the mouse. They demonstrated that the gene is a member of the SRC family of protooncogenes and concluded, on the basis of its preferential expression in B-lymphoid cells, that it functions in a signal transducing pathway specific to this lineage.

Pathology

- In man, chromosome abnormalities, deletions, or translocations are seen in 1p34 in neuroblastomas and in non-Hodgkin lymphoma. Rearrangement of LCK may play a role in lymphocyte malignancy and in these cases the levels of LCK mRNA are greatly elevated.
- Individuals with mutations in the gene coding for ZAP70, p56(lck) or p59(fyn) proteins show severe combined immunodeficiency (SCID) due to selective T-cell defect.
- Mice lacking p56(lck) as well as transgenic mice expressing dominant-negative mutations of p56(lck) demonstrate severe T-cell developmental defects.

Src Family

