

# **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

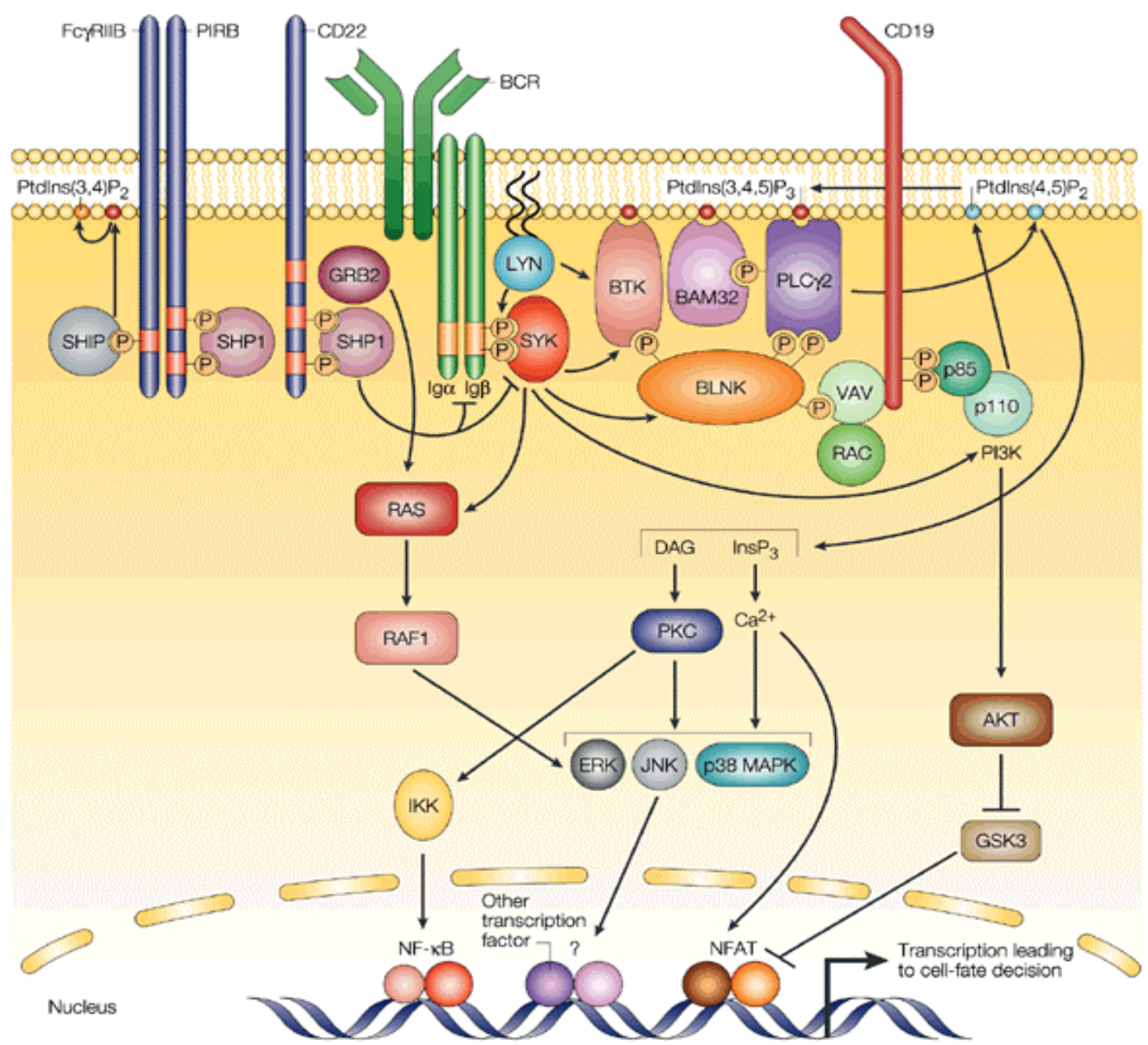
TEC family  
Btk

**Activated upon TCR  
engagement**

SRC Family  
Lck  
Fyn

SYK Family  
Zap-70

CSK family  
Csk

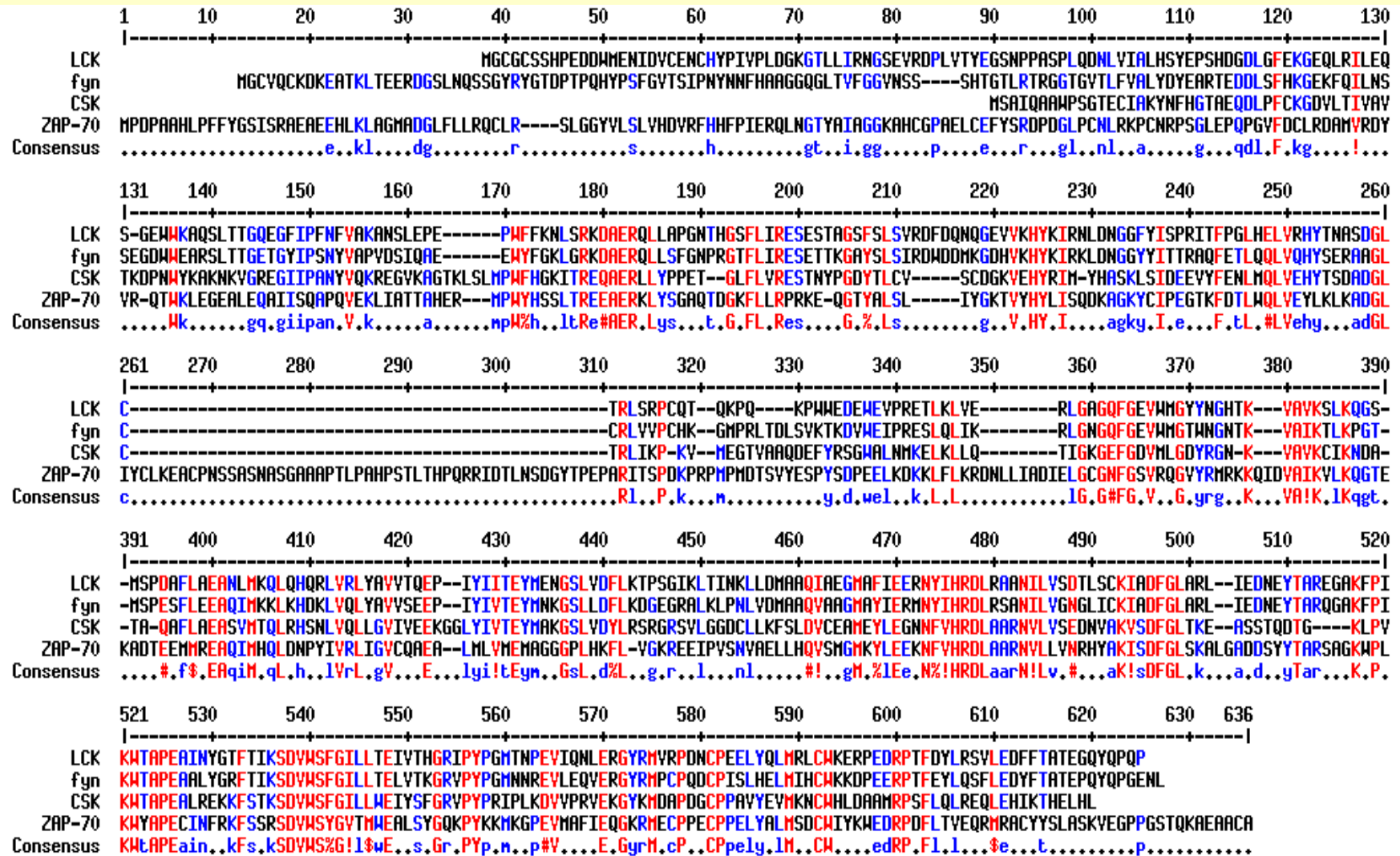




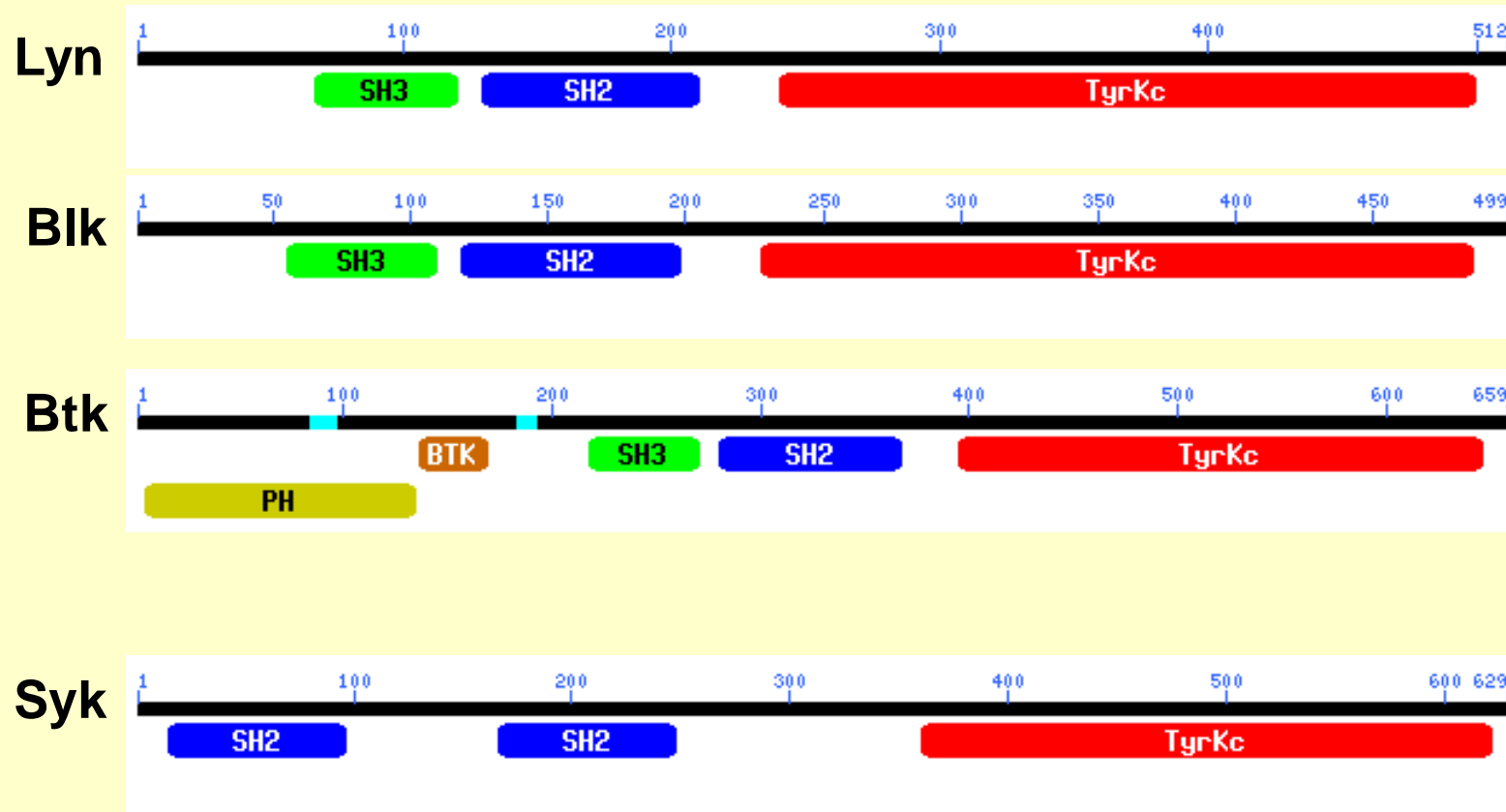
	1	10	20	30	40	50	60	70	80	90	100	110	120	130
	-----													
Lyn														
BLK														
BTK	MRAVILESIFLKRSQQKKTSPLNFKKRLFLLLVHKLSSYYEYDFERGRRGSKKGSIDVEKITCVETVIPEKNPPPERQIPRRGEESEMEQISIIERFPYPFQVYVDEGPLYVYFSPTEELRKRNIHQKLN													
SYK	MAGSAVDSANHLTYFFGNITRREAREYDLVQGGMTDGLYLLRQSRNLYGGFALSVAHNRKAHHYTIERLNGTYAI---SGGRAHASPADLCH---YHSQEPD													
Consensus	.....v.....y.f.....r.....v.....i.....g.....sp.....q...													
	131	140	150	160	170	180	190	200	210	220	230	240	250	260
	-----													
Lyn	MGCICKRKRKDNLNDDDEVDSKTQPVYRNTDRTIYVYRDPSTSNKQQRVPVPEFHLLPGQRFQTKDPEEQGDIYVVALYPYDGFHPDDL SFKKGEKMKVLEEHG-EHWKAKSLSSK													
BLK	MGLLSSKRQVS---EKKGMSPVK----IRTQDKAPPPLPPLVYFNHLAPPSPNQ--DPDEEERFVVALFDYAAVNDRLQVLKGEKLQVLRSTG-DWHLARSLVYG													
BTK	VIRCNSDLVQKYHPCFHIDGQYLCCSQTAKNANGCQILENRNGSLKPGSSHRKTKKPLPPTPEEDQILKPLPEPTAAPTISTTELKVVVALYDYNPMNANDLQLRKGEYFII EESNLPWRRARD-KNG													
SYK	GLICL--LKKPFNRPPGVQPKTGFPEFDKENLIREYVKTWNLGGQALEQAIIISQPKLEKLIATTAHEK-MPMFHGNISRDESEQTVLIGSKTNGKFLIRARDNSGSYALCLLHEGKVLHYRIDRQKTG													
Consensus	...c...l.....g.....n.....k..n.....i..qkp...kl.....k..P.....e.#...v!al..y..f..rdl...kge.l..L.e.....wra...ktg													
	261	270	280	290	300	310	320	330	340	350	360	370	380	390
	-----													
Lyn	REGFIPSNVYAKYN-TLETEEWFKIDITRKDAERQLLAPGNSAGAFIIRESETIKGSFSLSVRDYDPMHGDVIKHYKIRSLDNGGYYISPRITFPICISDIKHYKQSDGLCRRLKACISPKPQKP---													
BLK	REGYVPSNFVAPVE-TLEVEKWFRTISRKDAERQLLAPNKAQSFIIRESNKGAFSLSVKDIITQ-GEVYKHYKIRSLDNGGYYISPRITFPITLQALVQHYSKKG DGLCQKLTLPVNLAPKNL---													
BTK	QEGYIPSNYITEAEDSIEHYEYSKHMTRSQAERQLLQEGEKGGFIVGDSSKAGKYTVSVFAKSTGEPQG-VIRHYVVCSTPQSQYYLAEKHLFSTIPELINYHQHNSAGLISRLKYPVSKQKNAPSTA													
SYK	KLSIPEGKFFDTLMQLV EHYSYKPDGLLR----VLTVPCKIGAQHGHPGSPNNAHPVTHSPGGIISRIKSYSFPKPGHKPPAPPQGSRPETVSFNPYEPTGGPMGPDRGLQREALPHOTEVYESPYAD													
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	-MDKDAWEI--PRESIKLV-KKLGAGQFGEVWNGYNNST---KVAVKTLKLGTHSV---QAFLEEARLHKTLQHDKLVRLYAVVTKKEPIYIITEFMAKGSLLDFLKSDEGGKVLPLKIDFSAQIAREG													
BLK	-MAQDEWEI--PRQSLKLV-RKLGSGQFGEVWNGYNNKNN---KVAIKTLKEGTMSV---EAFLEEARVHKTLQHERLVRLYAVVYTR-PIYIITEYMARGLLDFLKTDEGSRLSLPRIDMSAQVAREG													
BTK	GLGYGSAWEI--DPKDLTFL-KELGTFQFVYKYGKRRGQY---DVAIKMIREGSHSE---DEFIEEARVHMLSHKLVQLYGVCTKQRFIITEYMARGLLNYLR-ENRHRFQTQQLLEHCKDVCER													
SYK	PEEIRPKEVYLDORSLTLEDNELGSGNFGTVKKGYYQMKVYKTVAVKILKNEANDPALKDELLAEANVMQLDNPYIVRHIGICER-SAMLVMEAEELGPNKYLQ--QNRHIKDKNIIELVHQVSHG													
Consensus	.....WE!..dr..ltl...eLGS#FG.Vk.Gyy.....VA!K.lk.g.nsp...#efl.EANVM..L.h..lvr\$yg!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	MAYIERKNIHRDLRAANLVSESLMCKIADFGLARIIIDNE--YTAGAKFPKHTAPEAIFGCFITKSDVMSFGILLYEIVTYGKIPYPRGTNADVMSALSQGYRMPRMENCPDELY-DIMKMCWK													
BLK	MAYIERMNSIHRDLRAANILVSETLCCKIADFGLARII-DSE--YTAGAKFPKHTAPEAIFGVFTIKADVMSFGVLLMEIVTYGRVPYPGMSNPEVIRSLHEGYRMPCPETCPPELYNDIITECWR													
BTK	MEYLESKQFLHRDLAARNCLVNDQGVVKVSDFGLSRYVLDE--YTSVSGSKFPVRSPPPEVLVMSKFSKSDIHAFGVLMHEIYSLGKMPYERFTNSEARAEHIAQGLRLYRPHLASERVY-TIMYSCWH													
SYK	MKYLEESNFVHRDLAARNVLLVTQHYAKISDFGLSKALRADENYKQATHGKMPVKHYAPEICINYYKFSKSDVMSFGVLMHEAFSYGQKPYRGMKGEVTAHLEKGERMCPAGCPREHY-DLHMLCWT													
Consensus	M..YIE..#f..HRDLaARnLv...q...K!sDFGLsr...dde...Ytaq.g.KfP!k.a.pE.in%.kFssKsD!HsFG!L\$uEi.syG..PY.gn.ns#v...le.G.R\$.cp...cp.e.Y.din...CH.													
	651	660	670	681										
	-----													
Lyn	EKAEEERTFDYLSVLDFFYTATEGQYQQP													
BLK	GRPEERTFEFLQSVLEDFYTATEGQYELQP													
BTK	EKADERPSFKILLSNILDVHDEES													
SYK	YDVENRPGFTAVELRLRNYYDVVN													
Consensus	...#RP.F..l.s.l.#.y.....													

	1	10	20	30	40	50	60	70	80	90	100	110	120	130
Lyn	MGCISKRRKDNLNDDVEVSKTQPVYRNTDRTIYVRDPTSNKQQRVPVEFHLLPGQRFQTKDPEEQGDIYVALYPYDGFHPDLSFKKGEKMKVLEEHGEAMKAKSLSSKREGFIPSNYVAKVNTLETEEWF													
BLK	MGLLSKRQVS---EKKGKMSPVK----IRTQDKAPPPLPLVVFNHLAPPSPNQ--DPDEEERFVVALFDYAAVNDRLQVLKGEKLQVLRSTGDWHLARSLVTGREGYVPSNFVAPVETLEVEKWF													
Consensus	MGCiSKRQdn....EkdkgtqPvr.....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	FKDITRKDAERQLLAPGNSAGAFLIRESSETIKGSFSLSVRDYDPMHGDVVKHYKIRSLDNGGYYISPRITFPICISDMIKHYQKQSDGLCRRLEKACISPKPQKPDWDAWEIPRESIKLYKKLGAQQFGE													
BLK	FRTISRKDAERQLLAPMNAKGSFLIRESESNKGFSLSVKIDITTQ-GEVVKHYKIRSLDNGGYYISPRITFPTLQALVQHYSKKGDGLCQKLTLPVNLAPKNLWAQDEWEIPRQSLKLYRKLGSQQFGE													
Consensus	FrdIsRKDAERQLLAPgnkAGaFLIRESEsnKGFSLSVrDidpq.G#V!KHYKIRSLDNGGYYISPRITFPciqa\$!qHYqKqgDGLCrrLelaC!nlaPqnIWAQDAWEIPR#SiKLYrKLGAQQFGE													
	261	270	280	290	300	310	320	330	340	350	360	370	380	390
Lyn	VMGYYNNSTKVAVKTLKLGTHSVQAFLEEARLIMKTLQHQKLVRLYAVVTKEEPIYIITEFMAKGSLLDFLKSDEGGKVLPLKLIIDFSAQIAEGMAYIERKNYIHRDLRAANVLYSESLMCKIADFLGLAR													
BLK	VMGYYKNMMKVAIKTLKEGTMSPEAFLEEARVMKTLQHERLVRLYAVVTRE-PIYIVTEYMARGCLLDFLKTDEGSRLSLPRLIDMSAQVAREGMAYIERMNSIHRDLRAANILYSETLCCKIADFLGLAR													
Consensus	VMGYYnNnmKYA!KTLKeGTMSp#AFLeEARLIMKTLQH#rLVRLYAVVTRE.PIYI!TE%MARGcLLDFLKSDEGgrlLPrLIDnSAQ!AREGMAYIERknsIHRDLRAAN!LYSESLcCKIADFLGLAR													
	391	400	410	420	430	440	450	460	470	480	490	500	510	513
Lyn	IIEDNEYTAREGAKFPIKHTAPEAInFGcFTIKSDVMSFGILLYEIVTYGKIPYPGRtNADVMSALSGYRMPRMENCpDELY-DIMKMCWKEKAERPTFDYLQSVLDDFYTATEGQYQQP													
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

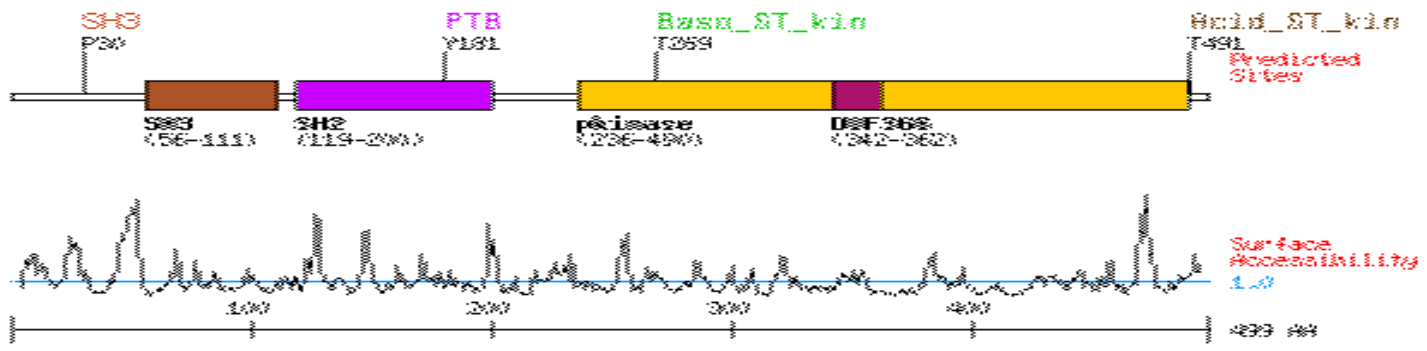
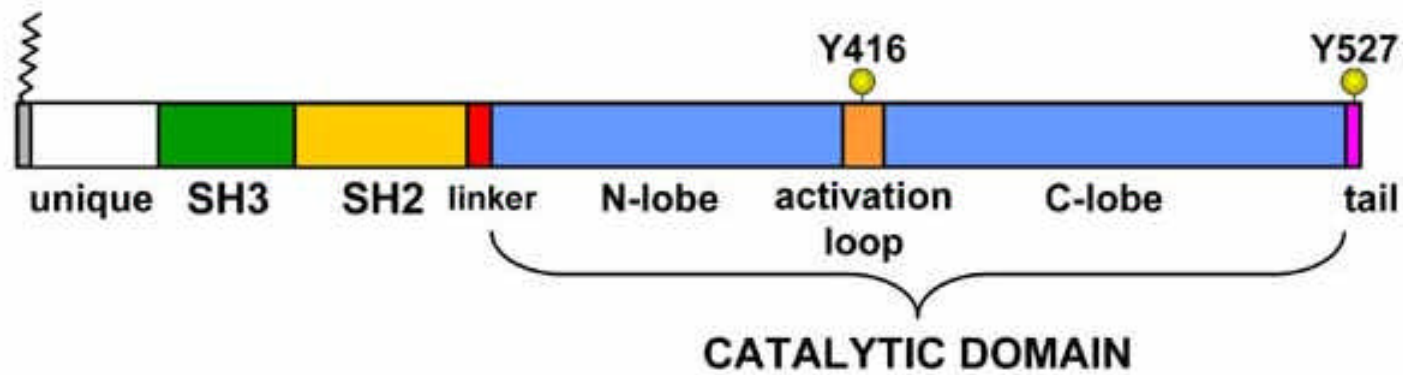


ZAP-70

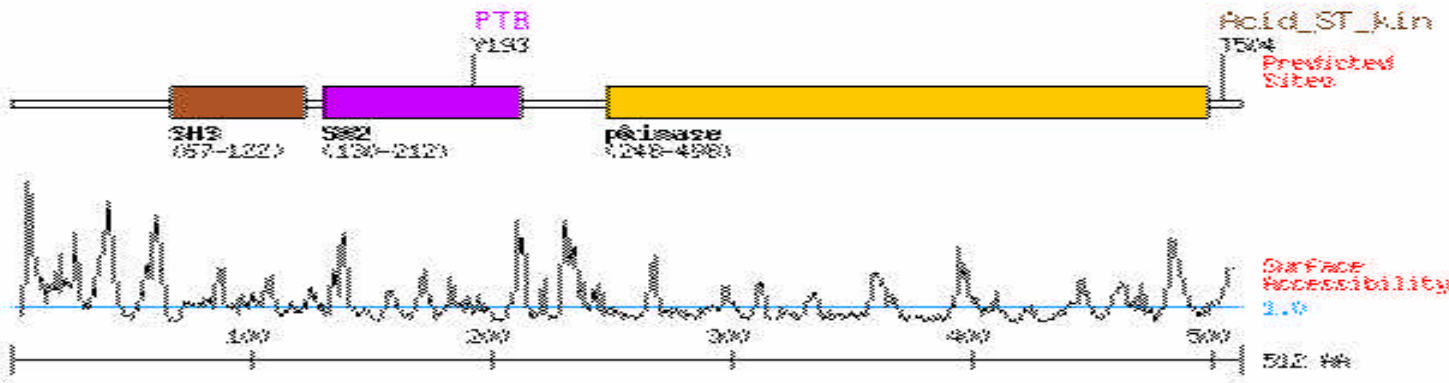


CSK

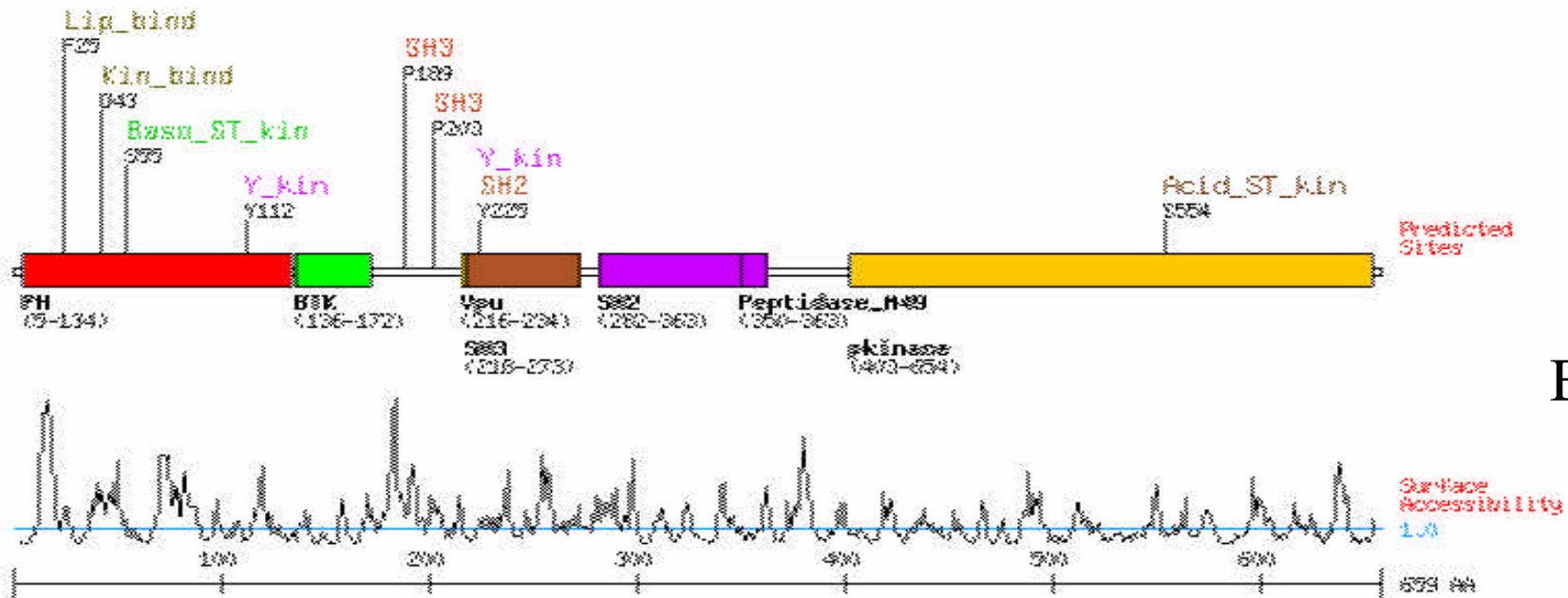
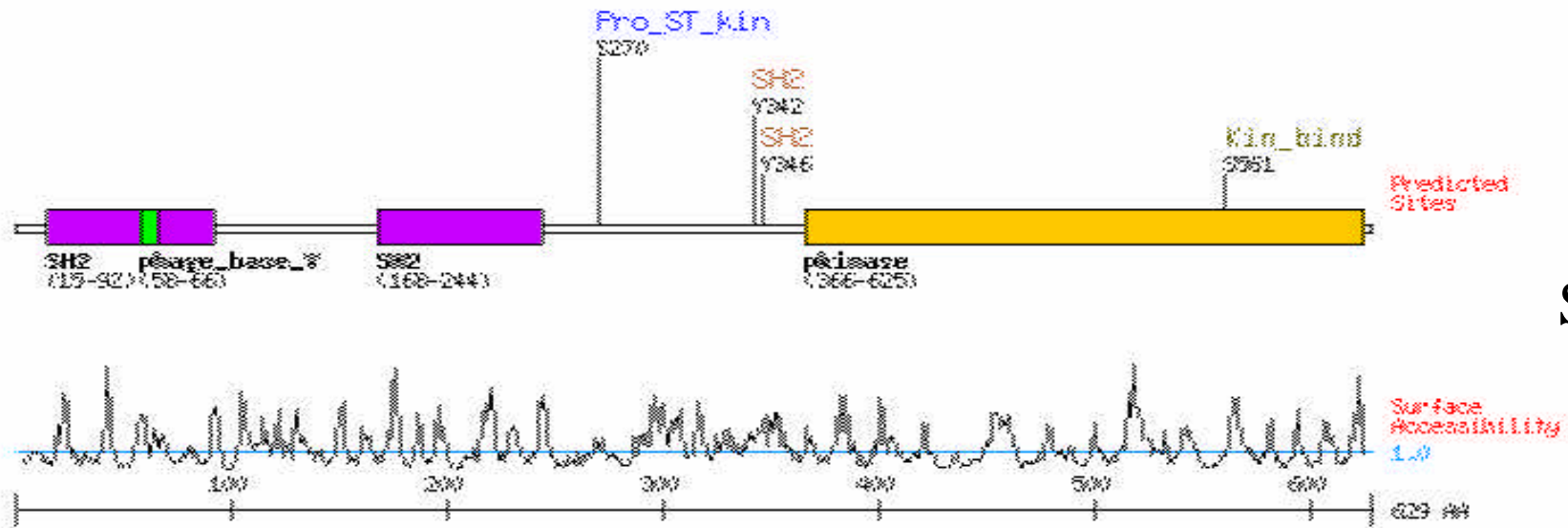




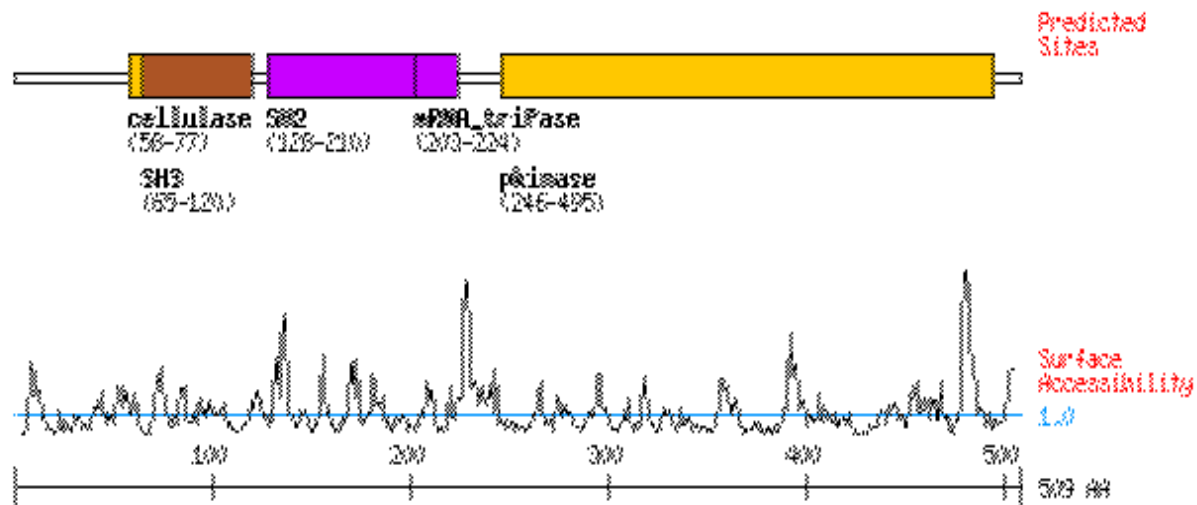
BLK



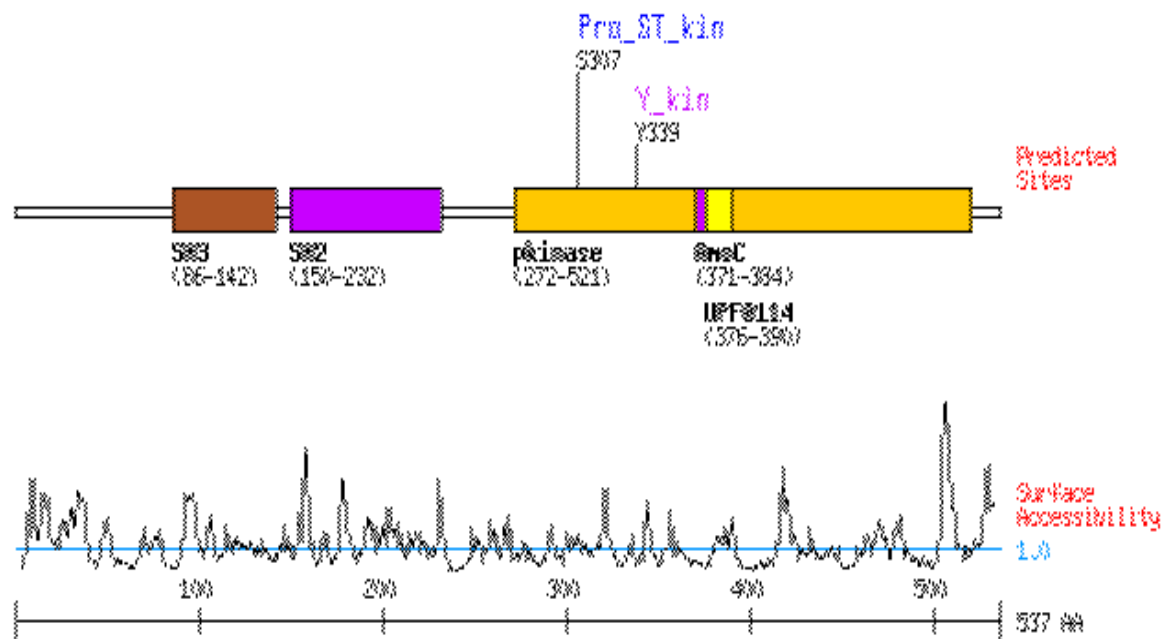
LYN



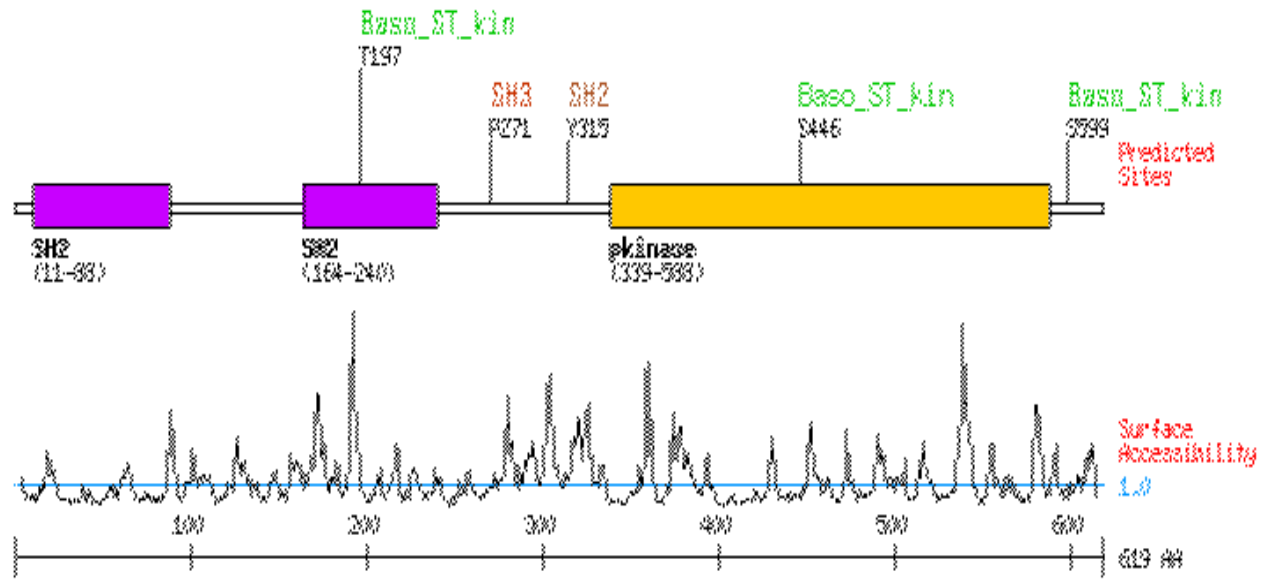
# LCK



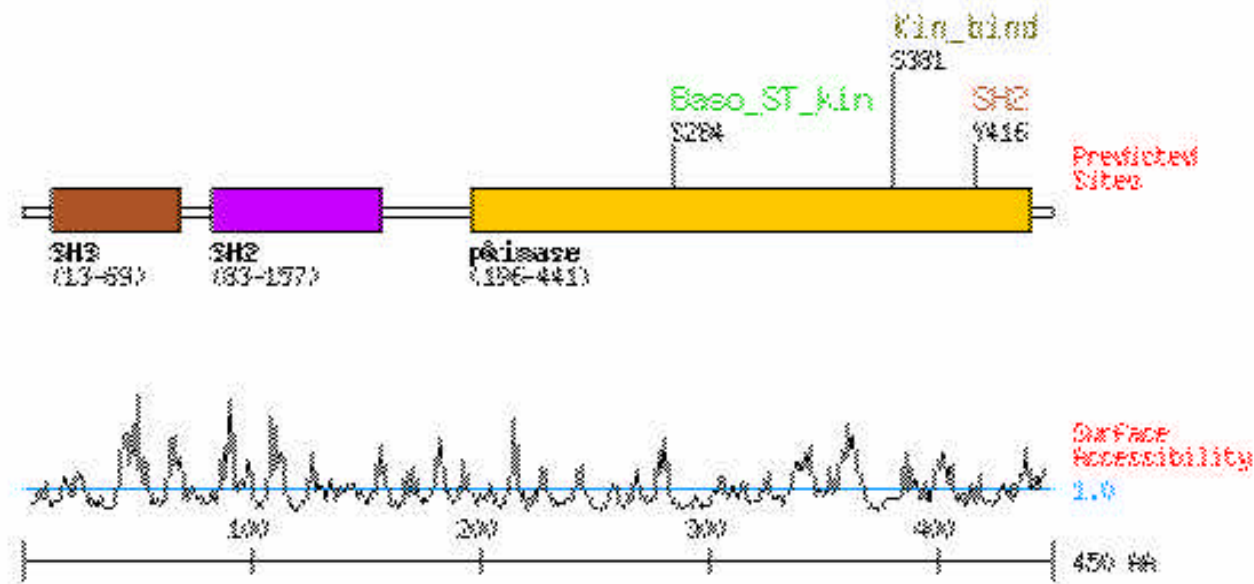
# FYN



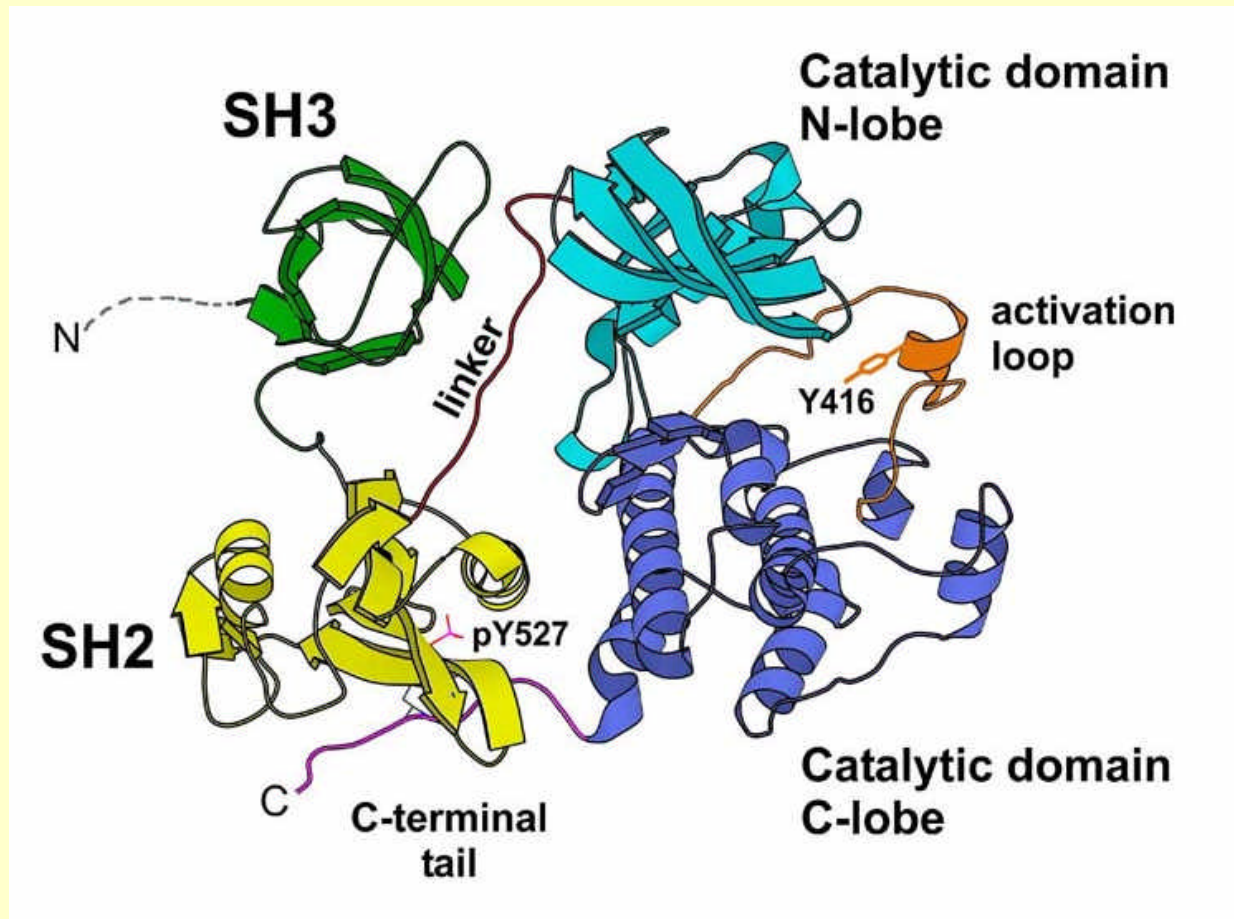
# ZAP-70



# 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 <b>Y</b>
			186 - 193	Rsl.Dngg <b>Y</b>
			390 - 397	RiieDne <b>Y</b>
			514 - 520	
Syk	32 - 37	GMtdGL	170 - 178	ReeaErkl <b>Y</b>
			190 - 198	RprkEqgt <b>Y</b>
			240 - 248	KlkaDgli <b>Y</b>
Blk	2-7	GLIsSK	174 - 181	Rsl.Dngg <b>Y</b>
			377 - 383	Rii.Dse. <b>Y</b>
			440 - 446	Rsl.Ehg. <b>Y</b>
Btk	50 - 55	GSkkGS	503 - 511	KdvcEame <b>Y</b>
			544 - 551	RyvIDde <b>Y</b>

# 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

