

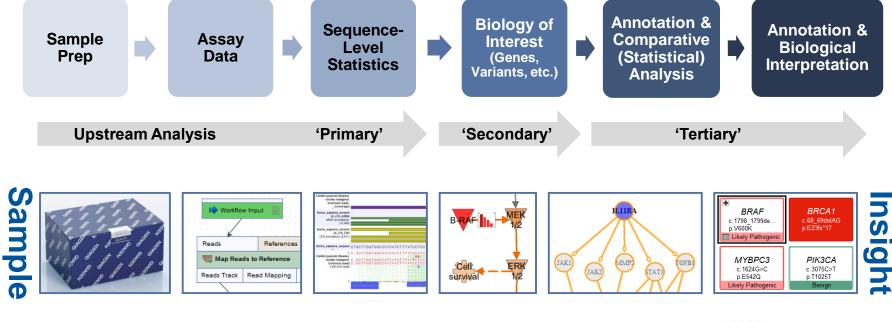
Normal	4078100	20194	Chr.	Position	Gene Region	Gene Symoo		100	in-frame						
* Confidence II 1387898 Exercise III 1397897 Conti, Markin KAMPFA MAR (191898 III III 1397897 Conti, Markin KAMPFA MAR (191898 III IIII 1397897 Conti, Markin KAMPFA MAR (191898 IIIII IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII		л			Exonic, Intro	nii Kilaad754, M	IAC p.V1305_A1306								
* Confidence 1 3879777 Boole, lattern KMA774, Latter pP1348 - is dram * Confidence - 1 101212755 Dank: lattern KMA774, Latter pP1348 - is dram * Confidence - - - - - is dram - - - is dram * Confidence - - - - - is dram - - - - - - - - - - is dram -		V	-		Exonic, Intro	nii KIAA0754, M	LAC p.11308S	-							
40/7640 1 101021978 Book G4442 \$15253888 - isseade 32053 1402 - 1 1122225 3076 Book Book Biok Biok <td></td> <td></td> <td>1</td> <td></td> <td>Evonic Introl</td> <td>nix KIAA0754, M</td> <td>IAC p.P13145</td> <td>-</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>			1		Evonic Introl	nix KIAA0754, M	IAC p.P13145	-							
** Commo Variants	4077848	20194	1				p.152_153insS*	-							
* Common Variante 2/00 1 1000/101 2000/101 1000/101 2000/101 <		Û	1				p.11358fs	-				11	116158152		
34353 Lucz 17944023 Exak TN PLAZP, PLAZ missee Duriper musee Duriper N Predicted Berg Biological Context 2 2/175472 Exak PVR6 L/12P, PLAZ - data data - missee Duriper musee 0.004Per	- Nat	iants E0	1				p.E10236fs, p.E	-	The second s						
Subset Biological Context 2 17940233 Exame Initiative		14902 **	2	179539770			p.R2074W, p.R2	-		Damaging	unnell				
No. Discription 1 1 2 2 1 1 <th2< th=""> 2 <t< th=""><th>345055</th><th>at legical Context</th><th>2</th><th>179640233</th><th>a second and</th><th></th><th></th><th>-</th><th>Wissense</th><th></th><th>microRNA Bindir Mikz rok</th><th></th><th></th><th></th><th></th></t<></th2<>	345055	at legical Context	2	179640233	a second and			-	Wissense		microRNA Bindir Mikz rok				
× Prediced Common Variants 3 25/93/22 Euric NCA P/39 massee realware Vision Anone Vision Anone P/39 - massee realware Vision Anone P/39/20 EURic - massee Paral Vision Addres Vision P/39/20 EURic - massee Paral Posicial Location 1 24/0472 Vision P/199/20 P/39/20 - massee Paral parale - massee Paral parale - massee Paral parale - - parale - - - - - - - - -		Biological Contents	3 3	12475472	Exonic			-	1			29	1801165		
850 Continent call 10 9759702 Examic RC E 12990, PE1 Initiation massace Duraging 2014 Continent call 1 12175242 Examic RC PE3940, PE31 Initiation 1 1 2014 Pharmacogenetics 0 26077061 20176 Contine RC PE344G Initiation 1 Initiation 1 Initiation 1 Initiation 1 Initiation	× Predicted	Cancer Driver use	2	25639332	3'UTR		p.Y39*	-		Tolerated					
Visited Annotation 112/17/242 Levic ROR2 EER4 Image: Company interval inter			ľ.		Exonic			-		Damaging	nuu Rindii MIR300, MIR381		ca10128		
Kenetic Constraints Particular Particula			Ē		Exonic			-	Witzense		microRNA Bindii MR361		5030320		
Vertice 0 256/7701 3///k C//k = aments Damage 3 Biblioter 1 3240472 3//k VF p 1998, p 24 = aments Damage 3 Biblioter 1 3240472 3//k VF p 1998, p 24 = aments Damage 3 Decide Data 1 654097 20//k VF p 1998, p 24 = aments Damage 3 Decide Data 1 654097 20//k VF p 1998, p 24 = aments Damage 3 Decide Data 1 654097 20//k VF p 298 aments Damage 3 Decide Data 12 1233726 Exolit VF p 297 mission p 207 mission p 207 mission mission Damage 1 1 100 mission mission Damage 17 1774000 Exolit p 207 10 mission g		Custom Analysis	Ľ					-			microkveccus	1			
Physical Location 1 32409472 3UTR N* p.p1986, p.P48 is drave Dampin 20 Bradiscal Association 1 6454001 1 6454001 - nitration 20 Badiscal Association 1 6454001 10 645001 - nitration 21 Display Location 1 645001 10 6020227 - - nitration - nitration 24 Display Location 15 6020227 - - nitration - <t< th=""><th></th><th>Genetic Analysis</th><th></th><th></th><th></th><th></th><th></th><th>-</th><th>frameshift</th><th></th><th></th><th>2</th><th>H</th><th></th><th></th></t<>		Genetic Analysis						-	frameshift			2	H		
Producted Deterious 1 664/0017 Bond 91 9253	200	Pharmacogene	1				p.P199fs. p.P48	-							
Statistical Association 12 12/33/752 Eular Fait p.11/2 in missee Dumping Add Finer 15 6690/327 Eunic, IndRiv SLOB p.01/244, p.01		Physical Collectoriou	s					-		Damaging					
User-Defined Valuation 15 4900222 Exolution P247/s misterioris Add Filter 15 66992733 Exolution Exolution attraction attractraction attraction <td< th=""><th>× Biological</th><th>autiotical Associau</th><th></th><th></th><th></th><th></th><th>p.S115C</th><th>-</th><th></th><th>Distance</th><th></th><th></th><th></th><th></th><th></th></td<>	× Biological	autiotical Associau					p.S115C	-		Distance					
Add Table 15 6509733 Examine greep 1 EUTream 10 Ept 1 Dest	25	Stausucure Defined Varian	ts					-	missense	Dauradana					
Add Table 15 December 9FEEP DE12*				cc005733		INA SMADO	p.D1124N, p.D1	-	stop gain				(0)		
		Add Filler		47716010	1777 . Am	SKED	p.E12*	-				1	-		
						SREEF		-		-		-			
INGENUITY				17 1/14000						-					
INGENUITY								1				>			
INGENUITY				-	-			1				5			
INGENUITY	-	5		-	-							-			
INGENUITY	· Committee		-	-	-			1	-						
INGENUITY				4				-		-					
INGENUITY							-	25							
INGENUITY				E	1	1		-							
INGENUITY	1					-									
INGLINUTTI	1				-										
		N VIIIII													
		1 million					00		-						
VARIANT ANALYSIS						-	Contra to		No.		ΝΛΑΡ	1 /		ΔΝΔΙ	VCIC
VANANT ANALISI.						1-1	1	1	N.						

Finding Causal Variants Using Ingenuity Variant Analysis (IVA)

Dev Mistry, Ph.D. Field Applications Scientist Devendra.Mistry@qiagen.com



QIAGEN Sample to Insight













Sample to Insight



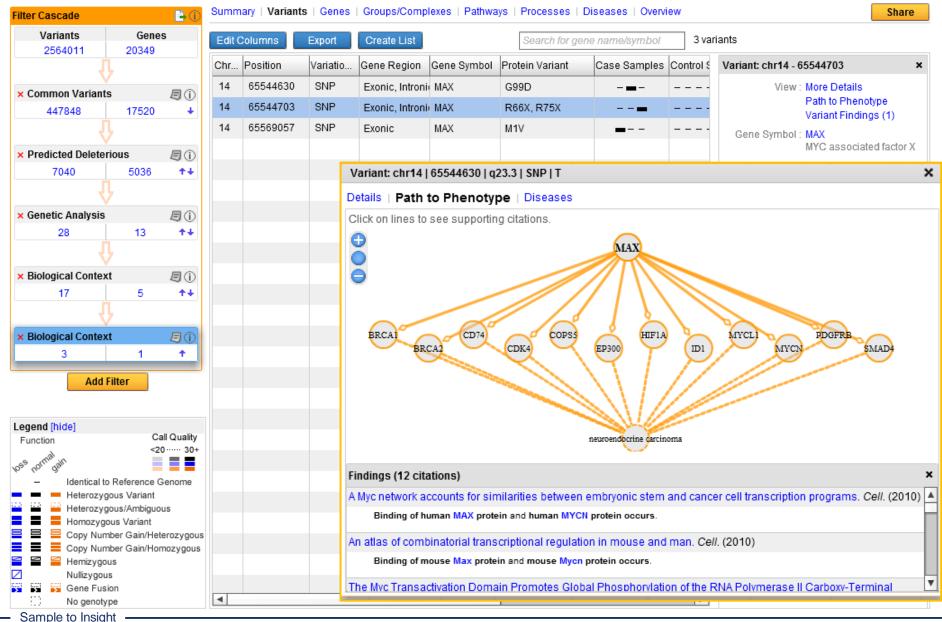
- Introduction
- Data upload and sharing process
- Analysis filter setup
- Results and biological interpretation
- Exporting results
- Summary



What is Ingenuity Variant Analysis and why use it?



Efficient Cascade to Biologically Meaningful Variants





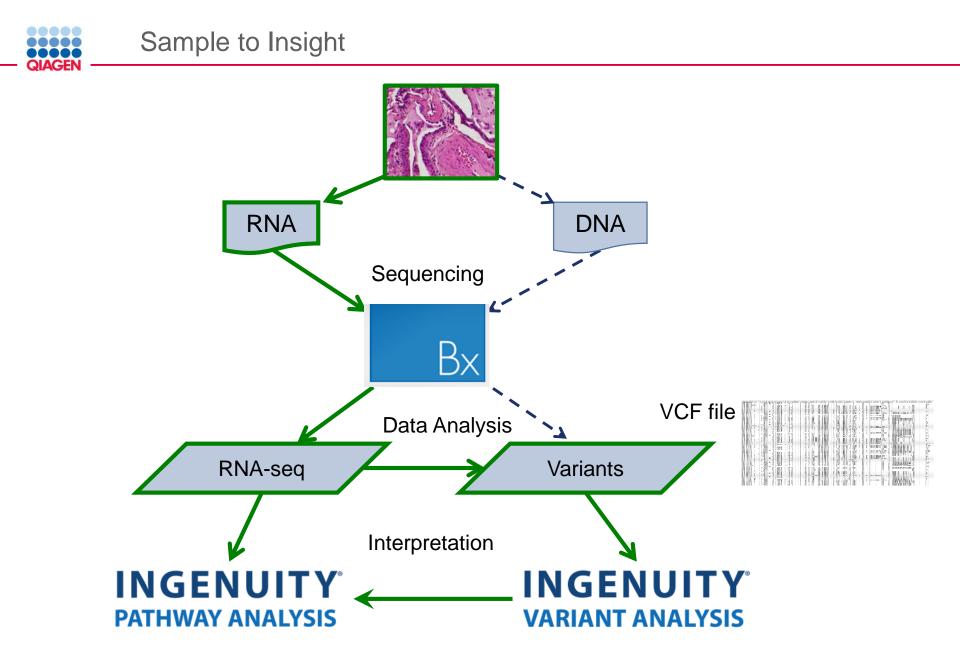
Simply not scalable...

		3 28 aubalitat 0.043	31 2		a .		 14.3	172	5					,			PALSE	-d -d Hageabria	-4.275		P, GP, HS
1.5E-87 1.5E-87 G A	21	15 71.4286 autolitat 0.003	22 3 ++725135 5.	- SHE G A	A 87.8555	1924	 16.41	338	5								PALSE	d d Hagealeia	1.175		HS
1.52-87 1.52-87 C A		2 SS.SSS2 autoritat ILIN	45 2		- 4	- 4	 1.25		3								PALSE	-1 -1 Bagealeia	1.515		97,P,H,H
1.7E-82 1.7E-82 TTT&TTTGTTTG	c ،	S R.S deletion 1	I I ++121620 0-		G, A, -, TT -1	- 4 - 1	 2.17				1.72-17 1.72-17		I UTR		36643		PALSE	-1 -1 Hagealeia	1.465	1 517531	6V,P,HS
1.7E-87 1.7E-87 G T	22	25 15.052	23 11115201 5.	- SHE G T	T 22.002	338	83.65		S XKRS HH_S		1.78-17 1.78-17 -		S EXON_R	4 1.76-87 1.76-87		14 E.4.57 H H	PALSE	442 1 HH_ 4758 4324637 HETYPE H -> H [], JISHP;5748 525 1 HH_ 4758 585436 HETYPEEHDEES' H. Junio	21. 4.412	El bilg//www.anki.alu.aik.gan/rabres/dispanin.a 159165	E,HS
1.7E-87 1.7E-87 A G		15 58 and all all all all all all all all all al	26 10 +114305 54	USHFA G	G 82.1231	212	58.86		S XKRS HH_S S XKRS HH_S		1.75-17 1.75-17		S EXON_R	4 1.75-17 1.75-17		11 E+4-174 F		255 I HH_1751 7658-C HETYPECHDEES H. Jackin 255 I HH_1751 7658-C HETYPE P->L (in TRANSM H-1	1.1	Kilg://www.anki.ela.elk.gom/wiley/dispanines 159455 22 Kilg://www.anki.ela.elk.gom/wiley/dispanines 159455	E,P E.HS
1.7E-87 1.7E-87 G A		41 \$1.114 eshelided	21 12		8 4,211	146	51.51	711	S XXRS HH_S		1.75-17 1.75-17		3 EXON R	4 1.75-17 1.75-17		11 E-4-114 P	PALSE	232 2 HH_1751 ESSGA HETYYE POLIA (RANSPIN)		10 Mig://www.aski.ala.aik.gon/edree/Nigenia.a 150165	E.P.HS
17E-IP 17E-IP C T	135	116 111 askalidad I	25 11		T IR.2314	201	12.35		S GARM MH B		126-12 126-12	i i	1 EXON R	6 1.7E-IR 1.7E-IR		65 E+6-2 K K	TRUE	425 I HH 1010 1202C>T HSLPSPSPSRELCE He downline	1.05	1 (2054	E
1.7E-87 1.7E-87 G A	17	16 53.2533balilal B	27 7 ++539268 5.	- SHE G A	A 38.5283	1857	 41.85	483	S GAD4 MMLB	111 45285	1.72-17 1.72-17	- 18	18 EXON_R	1 1.72-87 1.72-87	177 2	II E.J.JI H H	TRUE	178 B HH, BHI SIBGA HSLPSPSPSRELCE H. Jamain	-8.281	1 12154	E
1.7E-87 1.7E-87 C A	11	3 38 autofiliet 8.882	21 1 ++215124 5.	- SHE C A	A 33.7453	765	 22.44	259	S GAD4 MHLE		1.26-12 1.26-12 -	- 11	18 EXON.R	1 1.78-87 1.78-87	200 2	II E.1.7 G	PALSE	151 1 HH, BHI 407CHA HSLPSPSPSRELCE H. Annala	-8.997	100 12054	E.S.HS
1.8E-82 1.8E-82 C T	12	73 36.3415 aubalitat 8	22 15 ++224184 5.	- SHF C T	T 85.4558	4656	 33.67	1011	S IL 17RA HH_F	143 38734	1.15-12 1.05-12	11	13 SA_SITE	10 1.02-07 1.02-07	11	10 17510-10	PALSE	A A He avairie	-1.127	8 CO:8827 Jarllanet Mij://ac Candidia Cylobiae Ensirene Mij://ac 20765	55,HS
1.1E-17 1.1E-17 C T	28	1 41 1	16 4 + 171575 5.		T 10.5040	1635	 14.54			143 38734	1.12-12 1.12-12		15 EXON_R	11 1.12-17 1.12-17		14 E+15-371 I I		I HH_BIHS HISBCOT HGAARSPPSAVPC TOPO_D C.	1.155	1 CO2002 (pellanet blig://ac Candidia Cylobiae Basireen blig://ac 20765	E
1.1E-17 1.1E-17 C T	15	3 68 ankalilal 8	26 4 ++481955 5.		T 25.5959	1451	 16.5	155	S IL17RA HH_B	141 18794	1.12-12 1.12-12	- 11	15 EXON_R	11 1.12-17 1.12-17	1875 15	14 E.13-448 P P		TZE E HH_E145 ZIEBC>T HGAARSPPSAVPC TOPO_D C41	4.241	1 60:1117 (sell-set bilg://ac Castilia Cylobiae Essiesse bilg://ac 23765	2
1.82-87 1.82-87 G A	,	5 10 adalah 1.000	22 2 ++599262 5.		A 85.2185	3752	 66.82	248	5								PALSE	-1 -1 Hagealeia	8.556		0V,HS
1.8E-82 1.8E-82 C G		10 21.7331 autobiliat 0	23 5 ++163828 5+		G 2.6694	197	1.26	112	S CECRS HH_B		1.12-12 1.12-12 -		EXON_R	1 1.10-17 1.10-17		17 E.I.III R 5	PALSE	155 I HH_1171 1117C>G HY#W77LP5P5055 H. Januar	1.252	110 CO1001 [articlatic process]; 2740	E,P,H,H
1.16-17 1.16-17 G A 1.16-17 1.16-17 G A		96 22,2221 aubalitat 1,009	11 2		A 14.372 A 51.4331	4563	27.54				1.16-17 1.16-17		EXON R	2 10247 10247		59 1952-52 IN Ex2-55 G G	TRUE	-1 -1 Repeated	-1.19	If G0:IIII (Jarlahila process); 2740 If G0:IIII (Jarlahila process); 2740	HS
LIE-IZ LIE-IZ C R		11 S1.5625 askelided	21 7 122190 52		G 57,2224	1503	9.5				1.16-17 1.16-17	-	3 EXON R	5 1.1E-17 1.1E-17		11 E-6-31 H B	PALSE	12 INTERVIEW PERMIT AND A REAL AND A	1,213	21 GO:1117 [and Santa provide]; 2700 21 GO:1117 [and Santa provide] [parties ritherautors 51016	E.HS
LIE-17 LIE-17 a C		15 10 adalial I	27 7 121121 5		C 21.1126	1211	12.16		S CECRI MH S		11012 11012	;	7 UTR	1.1.1	20122		PALSE	d d Hamalaia	-1.111	I Statistical and the second development in the second sec	85
1.1E-17 1.1E-17 G A	21	22 78.5714 aubalilat 8.884	21 1		A 35.5241	3387	\$4.75				1.12-17 1.12-17		S EXON.R	1 1.02-02 1.02-02		22 E.1-157 H H	TRUE	55 I MM. \$174 153GA MUVDGPSERPALC REGION, DI-		1 CO188872 [multiarflater ergeningel deurteament][]earier eitensaten 51816	
1.1E-17 1.1E-17 G C	61	1 23.5102 unbalitet	12 4 ++728416 5.		C 52,7353	1586	 58.45		S CECR2 HHLE		1.10-12 1.00-02	- 11	1 INTROM	1 1.15-17 1.15-17		53 1753-43	PALSE	d d Hearairia	-1.435	1 90:000 Janualani Mila://www.anki.ala.aik.ana/ealera/diananin.a 2700	HS
1.8E-87 1.8E-87 T A	2	7 100 autoDat 0	24 4 ++622414 5.		A 4.1555	51 1	 1.55		S CECR2 HH_B	514 27210	1.12-17 1.12-17		1 INTRON	1 1.12-17 1.12-17		16 1758-22	PALSE	d d Happaleia	1.217	1 CO:11112 spepter: http://www.anki.alu.eik.gon/valere/disponin.a 27465	P,HS
1.10-17 1.10-17 A G		3 37.5 autolitat 1.886	21 2 ++121671 5.		G 21.5437	1154 1	 27.58	516	S CECR2 HH_B		1.12-17 1.12-17	- 11	1 INTRON	11 1.12-17 1.12-17		61 IV516-84	PALSE	-1 -1 Happaleia	-1.06	1 CO:11112 (spepter) blip://www.anki.atu.aik.gon/eaters/disponin.a 27445	97,85
1.1E-07 1.1E-07 A	11	E SELSESS deletion 1	I I +.356833 0.		nn d		11.51		S ATPSVIEL NHL		1.12-17 1.12-17		SA_SITE	2 1.10-12 1.10-12		10 1957-5	PALSE	-1 -1 He prairie	1.34	E GOURTES (ATP byd blig://www.anki.af Oxidalian Matabali blig://ww. 523	SS,P,HS
1.1E-17 1.1E-17 C T	5	5 100	21 5 ++225788 5+		T 12.010	1672	\$5.55	641	S DCL2L1S HH_B		1.12.17 1.12.17	1	E INTROM	3 1.10-12 1.10-12		78 1953-46	PALSE	-1 -1 Repeatein	-1.102	6 Go:11161 patientian of ecopore culturing (findmalian of epoptasing) or 23716	AR,97,8
1.1E-17 1.1E-17 A G	35	23 12.1571 auto6341 1.142	20 7 ++101990 5+		G 74.3553	\$552	59.55	618	S PID HH_1		1.12-12 1.02-02	-	E SA_SITE	4 1.10-17 1.10-17		10 1754-3	PALSE	-1 -1 Ha prairia	1.134	8 GO:1888 (protein f Ally://www.anki.af p53 nigna Cellator Ally://ww. 837	SS,HS
1.1E-17 1.1E-17 GCCRCGCTCRR(1.1E-17 1.1E-17 T C	· 11	2 10.1010 2-1-10-1		ARCTOC		- 4 - 1	11.11	127	5 DID HH_1		1.12-12 1.12-12	-	5 INTRON	1 1.05-02 1.05-02		86 1959-645	PALSE	-1 -1 Happaleia	1.61	8 GO:11161 (peaksin klip://www.anki.af p53 nigna Cellatar klip://we 632	P,OP,HS
CHE-17 CHE-17 T C	123	Et 43.5335 autolitat II 21 100 autolitat II	22 8 - 11999 5. 25 5 - 1599285 5.	r snFT C	C 5.2155	101	1.55	421	S PID HH_1 S HICALS HH_8		1.12-17 1.12-17 -		S EXON_R 31 EXON_R	3 1.12-17 1.12-17	116 2	11 E.3.16 S G	TRUE	18 1 HH_BH1 ZIT>C HDCEVH S > G[;, VAR_SE) H;, 725 8 HH_B152 S187T>C HEERKHETHINPA VAR_SE) H;,		SE GO:HHEI predvin klip://www.anki.af.p53 niged Critetor klip://wr E37 GO:HES5 publishin klip://www.anki.afw.aik.gom/refere/disputational 57553	E,HS
LIE-IP LIE-IP T C		24 fill anticidad in a	25 5 559285 5.	T THE T	c (1.121)	404	51.63	595			1.12-17 1.32-17	12	31 EXON_R	8 1.IE-IP 1.IE-IP	164 1	15 E.26-464 L L	TRUE	1 1 HH_BIS2 SINTIC HEERKHETHINPA VAR_SE-HL	-1.10	E CO1855 [anidalia http://www.anki.ala.aik.gon/velves/dispanie.s \$7555	
1.16-17 1.16-17 T C		23 35.3146 aubalitat	24 2 ++11112 5		C 42.5214	421	11.22				1.12.17 1.12.17		14 INTRON	11 1.16-17 1.16-17		IS 19513-2222	PALSE	-1 -1 Reprotein	4.00	COURSE (anidalia hilp://ana.anki.ala.aik.gon/valves/dispania.a 57555	MS
1.1E-12 1.1E-12 C T	111	SI (LIZE) ashelidad	27 5 ++211111 5+		T 1.055	24	11.07				1.15-17 1.35-17	ŝ	31 INTRON	15 1.16-17 1.16-17		15 17515-20	PALSE	d d Bapratria	-1.30	1 GO:1155 anidalia klip://ausu.anid.ala.nik.gon/valven/inponinta 57551	P,H,HS
	155	155 JJ.JSJ eshelilet	11 25 (411197 5)		8 111	2681	34.13				14647 14647	12	21 INTRON	11 1.16-17 1.16-17		62 17513-21	PALSE	d d Bagrateia	-2.112	1 GO:1155 midalin http://www.anki.alm.aik.gom/enters/dispanin.a 57551	85
1.1E-17 1.1E-17 T C	12	24 46.1538	25 5 283411 5.		c 54.5111	244	11.62				1.12-17 1.12-17	12	SI INTRON	1 1.12-17 1.12-17		54 1959-46	PALSE	d d Happania	-1.697	1 GO:1155 asidalia hilp://www.ashi.ala.aik.gon/estree/dispanin.a \$7555	HS
1E-17 1.1E-17 C A	22	5 22.2227	22 2			4	 				1.12-17 1.32-17	12	SI EXON.R	1 1.12-17 1.12-17		SI E.I.22 L L	TRUE	124 I HHLIHI 172CH HEERKHETHINPA REGION, H.		1 CO(1855) fanidalia bille//annu.anbi.elu.aib.ann/estere/disensin.a 57553	E.P.H
1.3E-87 1.3E-87 C T		15 18.25 aubalilat I	28 3 ++31000 5+		T 92.8949	1876	 4.15				1.12-17 1.12-17	44	I EXON R	\$ 1.30-87 1.30-87	26 1	47 E.6-26 T H		153 2 HH_1474 SIECOT HSKAPS T-> H (4-45HP-+34B	111.552	14 CONTINE Jabigaille bilge//aussanbilaturaik.gen/valees/diagonines 14274	E,OP,HS
1.3E-87 1.3E-87 G A	47	9 10 ada034 1	11 E ++4194 S.		A 23.3247	3185	\$2.63				1.35-32 1.35-32		IN INTROM	2 1.32-02 1.32-02		IN 1952-55	PALSE	-f -f Happaleia	1.61	1 CO:IIII: jaligaili, illy://www.asti.ala.aik.gan/valees/dispania.a 11274	HS
1.3E-87 1.3E-87 G C	n	5 22.7275 autoritati 1.000	15 5 ++107550 5+	- SHE G C	c 1		16.2		S GGTSP HR_H		1.32-67 1.32-67	13	I UTR		7997		PALSE	-1 -1 He prairie	2.999	1 G0:1116i (glatalkiner kinopalkelin peneros); 2523	67,P,H3
.3E-87 1.3E-87 CTCCAAG	1	E BL2145 deletion 1				1	 1.0		PRODE HH_		1.32-17 1.32-17	- 11	15 INTRON	3 1.32-87 1.32-87	135 3	94 IV\$9-49	PALSE	-1 -1 Hapraleia	1.465	8 GO:8886 gloland bllp://ww.Hyperper.Arginiar Melabali bllp://wc. 5625	AR,G,P,
1.3E-87 1.3E-87 A G	,	7 100 anticitat 1	21 1 ++223123 5+	ar SHE A G	6 41.4212	1972	 \$2.51		S DGCR2 HH_B	154 16429	1.32-12 1.32-12		1 INTROM	5 1.10-07 1.10-07	5741 68	11 1755-2388	PALSE	-1 -1 Hapraleia	-1.115	1 CO:III () (reapone bil) (//www.anbi.alw.aik.gon/ralers/diaponin.a 1999	HS
L3E-87 1.3E-87 T C		15 52.621 autorities	22 5 ++924285 5.	SHFT C	C 24.4991 G 4.6129	8	81.11	241	S DOCRIN DOCRIN MM_B S TSSK2 DOCRIN MM B	14333	1.32-82 1.32-82	- 11	18 UTR	1 135-8 135-8	318	7 5-1-11 K B	PALSE	-1 -1 Ha prairia	1.121	1 COUNTE Jakité prozening jikité ajining jipernan nyaka deuring 1220 25 COUNT hell défé bile://www.aski.ala.aik.asa/ealere/dimensiona 2052	HS
L3E-07 1.3E-07 A G		15 34.000 askeldal 1 33 23.221 askeldal 1	17 6 ++174785 5. 28 7 ++456841 5.	SHFA G	G 4.6129 T 45.4916	61	1.61		S TSSK2 DGCR14 HH_B S TSSK2 DGCR14 HH B	591 4046	1.3E-17 1.3E-17 -	1	1 EXON_R 1 EXON R	1 1.32-12 1.32-12		77 E-1-11 K R	TRUE	27 2 HH_1511 HAGG HODATVK-SR1. DOMAIN Pro 211 HH IS11 S15CST HODATVLRKKGYI DOMAIN Pro	2.274	26 G0:H11 pell 266 kllp://www.nki.ele.uk.gon/selees/disponies. 2050 H G0:H11 pell 266 kllp://www.nki.ele.uk.gon/selees/disponies. 2050	E,P,H,H
LIE-07 1.1E-07 C T	121	7 25.3253 aubalilal I	21 1	THE C	T 10.7461	105	21.11	151	S TSSK2 DGCR14 MH_B		1.32-07 1.32-07		1 EXON_R	1 1.32-87 1.32-87		77 5.1.112 5 5		251 I HH_ISSI 259CST HIDDATVLRKKGYI DOHAIN P.		E COMPERSIÓN (1977) and anti-ale ale anti-anti-anti-anti-anti-anti-anti-anti-	
1.3E-87 1.3E-87 C T		11 78.5714 aubalilat	10 7 105276 5.		T 24.5531	2485	23.74	274	S TSSK2 DGCR14 MPLE		1.12-17 1.32-17		1 EXON_R	1 1.32-87 1.32-87		77 E.1-237 T F	PALSE	28 2 HH_ 851 111CT HODAT'T - H (La ASHP - 4152		14 GO:1111 Jarll diff klip://www.anki.alu.aik.gon/enters/diagoniu.a 23642	E.HS
1.3E-87 1.3E-87 G A	11	12 111 anhalilal I	21 5 ++115277 5.		5116,15 A	1621	19.5	225	S TSSK2 DGCR14 MM.		1.35-17 1.35-17		1 EXON.R	1 1.35-87 1.35-87		77 E-1-58 R R	TRUE	142 I HH_ISSI 1825G>A HODATYLEKKGYI H. Jamain	1,247	1 69:000 forth diff billet//aussanbi.els.aib.aus/esters/discussion.e 20017	E.
1.3E-87 1.3E-87 C T		2 22.5HE	21 2 224811 5.		T 15.526	1411	23.65	275	S DGCR14 HH_B		1.10-12 1.30-12	- 11	IS EXON_R	1 1.15-17 1.15-17		15 E.J.22 E E	TRUE	151 I HH_ 1227 1859C>T HETPGASASSELLE H. domain	LIC	I GO:IIIII: Jakilik programing; [Rillik aplining]; [arranna agalem dearlay 1221	-
1.3E-87 1.3E-87 CCeG	25	3 12 delelies 1				- 4	 1.2	2	2 DOCK10 HH B	227 14333	1.35-12 1.35-12	- 11	11 EXON R	4 1.12-17 1.12-17		N 5.44 G G		157 2 HH 1227 (INCORCHETPGRESSLUE He densis	2.265	1111 CO:11112 =RMR processing RMR oplicing account system dearlag 1221	E,P,S,H
1.3E-87 1.3E-87 AT	1	6 15.7145 insertion 1	I I ++113185 0-	reland T	T,AT, -1	-4 -1	 51.63	582	S SLC2Se1 HR_8	336 2334	1.12-17 1.32-17	1	I UTR				PALSE	-1 -1 He profeio	1.775	1 60:11111 ailantar blip://www.anti.ala.aik.gan/esters/dispania.a 1575	P,HS
1.3E-87 1.3E-87 G T		14 16.2731 aukalitat 8	14 5			- 4 - 1	 8.55	•			1.10-17 1.30-17	,,	SZ EXON_R	23 1.35-87 1.35-87		24 E.23-33 Q K		1 HH_BITE ISTANT MAGILEVEPOENT REGION, N	5.667	53 COURTED Date and Ally//auso-metical Lynnesses Collator Ally://ar. 8248	E,P,C,H
L3E-87 1.3E-87 GT	21	10 12.3482 inneeline 1				- 4 - 1	 				1.32-17 1.32-17	33	SZ EXOH_R	28 1.35-87 1.35-87		11 E.28-55 H H		451 1 HH_1010 43715-GT HAGILPVRPQERP REGION, N.J.	4.411	100 CO:0000 Salesard Mig://asso.aski.at Lynnasso Cellater Mig://ast 1210	E,P,S,C,
1.3E-82 1.3E-82 T C	33	5 23.1763 ankalilat 1	23 6 ++186192 5.		c 96.099	1242	 \$2.45				1.32-17 1.32-17	33	SZ EXOH_R	25 1.30-07 1.30-07		68 E.25-24 H Y		1 HH_BHI SHET>C HAGILP" H-> V (* REGION, N->		21 GOSHIGI (Selever) Mily://www.anki.el Lynnama Cellelae Mily://www.1211	E,C,HS
1.3E-87 1.3E-87 C	36	SS 10 incedian 1	1 1 ++725544 0-		-,c,c, -4	- 4 - 1	 55.76				1.32-17 1.32-17	33		21 1.10-07 1.10-07		64 E.23-1 V V		201 2 HH_0010 SER2-C HAGILPVRPOENT-REGION, H-J		100 GO:0000 (internet Mily://www.anki.af Lynname Cellulae Mily://wr 1210	E,P,S,C,
1.3E-82 1.3E-82 C T 1.3E-82 1.3E-82 0 G	113	27 22.0031 autobiliat	11 7 ++121682 5.		T 8.5341	24	1.9				1.32-12 1.32-12 -	12	SI INTROM	11 1.10-07 1.10-07		5 19513-16	PALSE	-1 -1 Happaleia -1 -1 Happaleia	-1.65	I GOLINEE Entranet Elly://www.anki.af Equations Colletter Elly://www.1240	P,H,HS 55,P,H,R
1.3E-87 1.3E-87 H G		2 13.4515 anbalilat 8.888	24 12 141121 5-	ar SHE A G	•		1.17				1.35-17 1.35-17		ST EXON R	1 1.35-87 1.35-87		1 E-1-51 9 P	PALSE	41 2 HH BIT 12287-G MAGILPVRPGENT REGION, GL		76 GOLHER Salvard Mig//ausaniki.al Lannam Cellater Mig//arc 121	S,P,H,H
1.3E-82 1.3E-82 T G		S 11.1111 adalated 1				-	1.55				1.35-17 1.35-17		25 EXON R	11 1.35-17 1.35-17		62 E+13-24 K 9		THE REGION AND A CONTRACT OF THE REGION OF		21 SQUIII (Jane and All (Jane and All and Al	E.P.C.H
L3E-17 1.3E-17 C A		10 11.1111 establish	10 2	141 C 0	A 15,7651		5.46				1.36-12 1.36-12		25 INTRON	11 1.35-67 1.35-67		SE 19518-22	PALSE	-1 -1 Barralia	4.10	1 Stellin's particular http://www.anki.ala.ak.gov/rai/ra/rai/anania.a /201	E,V,C,M
1.3E-87 1.3E-87 G A		12 16.1616L-IG-I	21 52525 5.		A 23.1926	2313	22.55		S HRPLAN HHLM		1.12-17 1.12-17		4 EXON_R	1 1.15-17 1.15-17		25 E.4-38 R H		121 2 HH_1137 316God HTASYL R -> H (L. JLSHP 7575		21 G0:1011 [auduniad structure surplus result] 54176	E,AR,HS
1.1E-02 1.1E-02 G C	158	53 33,3333L-Ill-I	22 1 16 18 19 52 5.		C 7.4171	115	8.35		S UPD-IL HPLE		1.15-12 1.15-12	12	12 SALSITE	11 1.15-02 1.15-02		10 17510-20	PALSE	1 1 Hearalria	-1.112	E CONTRACT Jakeletal Allet//augumaki.al Pratrice Granital Allet//ar 2000	SS,H,HS
1.3E-87 1.3E-87 C T	117	67 35.8283 anbalilet	27 13 ++574574 5+	- SHF C T	T 45.3383	1365	 24.83	855	S UPD-IL HHLE	155 23275	1.10-12 1.30-12	12	12 INTROM	5 1.10-17 1.10-17	2559 25	78 1955-48	PALSE	d d Hearairia	-8.511	E 90:0011 Isheletat kila://www.ashi.at Peaksing Gearlist kila://wr 2353	HS
2E-87 2E-87 C T	33	31 33.3334 aubalitat 8	15 15 ++238155 5.	- SHF C T	T 34.85	5121	 33.13	383	S TRX1 HH_B	116 11630	28.47 28.47		I EXON_R	5 22-07 22-07	152 1	72 E-5-15 L L	TRUE	222 1 HH_BISS SEACOT HRISTYTROMERI DHA_BIP T-L	. LON	8 GO: HEEE (parallege bilg: //we Construent annualy fair equilation, 24 6833	
2E-87 2E-87 C T	12	11 31.007 B	21 1		T 2.2575	152	 1.13	1	4 CZZawFZI GHD4L C HH_B	246 8711			1 EXON R	1 22-17 22-17		15 E.J.(114 S S		SIN I HH_BING SIZCOT HERGECROOGER COMPENENT	G45 8.254	1 7350	E,P,H
2E-87 2E-87 T A	7	E IS.2103 autoritati II	14 \$ ++774488 \$.		A 2.5315	157	 1.0	- 1	2 CZZarf2! GHD1LC HH_B			,	1 EXON_R	1 20.47 20.47	282 18	15 E.1-282 T T	TRUE	258 B HH_B246 BS4T>A HPRGRCROOGPR COMPOS P++	44 -0.002	1 250	E,P,H
28-87 28-87 C T	5	< II	21 2 ++113375 5.	SHE C T	T 25.1181	\$24	16.46		S TXHRD2 HH_B			- 11	17 EXON_R	11 28-17 28-17	21	33 E.14-22 P P	TRUE	412 I HH_IIII 1215C>T HAAHAYALRGLG H. Jamain	-5.552	8 99:01116 (response billy)//www.anbi.al Parinidi Metaboli billy://wr 10507	E,97
2E-87 2E-87 A G		3 10 ada@at 1.000	27 5 ++115575 5.	- SHF A G	G 26,1192	3646	\$7.28	661	S TXHRD2 HH_B	164 66920		- 11	17 EXON_R	11 20-17 20-17		16 E+13-21 T	PALSE	2 HH_8864 11834-5 HAAHA' I-> T (% 465HP:++11937		13 GO:1111i Jeropana Ally://www.anki.al Parinidi Melakali Ally://w/ 11512	E,97,C
2E-87 2E-87 G A 2E-87 2E-87 A G	254	10 15.011 L-D-D I	11 1 - 511241 S. 11 1 - 61151F S.		A 5.6565	246	1.61		S TXHRO2 HH_B S TXHRO2 HH_B	164 66928	28-47 28-47		17 INTRON	11 22-07 22-07		42 19544-40 10 1950-64	PALSE	-1 -1 Happaleia	-1.557	1 CO:01112 (seepans Ally://accounting Payini)2 Heldeli Ally://ac 11507 1 CO:01112 (seepans Ally://accounting Payini)2 Heldeli Ally://ac 11507	H,HS
2E-87 2E-87 A G		4 10 1 1 10	10 1 - 115917 5.		G 72,7644	153	6.33	786			28.47 28.47 -		47 INTRON	1 22-17 22-17		III 1958-64 III 1959-1210	PALSE	-1 -1 He profess	-1.55	II GO:IIIII (respons http://www.aski.af Pyriailii Helsheli http://ww. 18587 II GO:IIII7 (results y http://ww.Sakiang/ Stevaid & Melsheli http://ww. 1942	HS
20-07 20-07 G N	12	5 21.4215 eshalilat	21 1		A 1.5532		1.55		LABYCE MM				17 SA SITE	5 20-07 20-07		11 1753-1211 11 1755-2	PALSE	-1 -1 He proleio -1 -1 He proleio	1.07	1 COUNTY preading http://ac.pakinegi.Stread & Pictabali, http://ac. 1912	55.97.8
25.42 25.42 1	1	2 III deleties 1				4					25.42 25.42		11 INTROM	2 25.42 25.42		77 1952.45	PALSE	-1 -1 Ha protein	LOI	1 GO:11311 Janimara Milat/Junus anti ala aikana/rairea/disamina 5002	97.2.1
2E-17 2E-17 C	21	25 35.5127 aubalidet	25 5 4115111 54		G (1.052	2012	56.05	656	S TRHTZE HH S			12	12 SD SITE	7 25-17 25-17		6 1752-7	PALSE	d d Happalois	-1.8	1 S9:1011: Jackahli Mat//assambiala.aik.am/edeen/dimenia.a 2702	55.85
22-47 22-47 T C		6 24.036	24 14175163 5.		c 24.555	334	31.5		S RANDPH NH		22.47 22.47		E INTRON	4 22-47 22-47		SB 1754-47	PALSE	d d Happalois	4.575	I GO:ING [internetInter transport][inigeal transford[ine]] 5302	85
2E-87 2E-87 TGTC	1	7 188 deleties 1	1 1		1. 100.00	-1	 \$1.75		S PHKAP1 NR_B		22-17 22-17	15	I UTR	1 1 1	2818		PALSE	d d Happaleia	3.887	1 60:11411 [phosphainesilide-medialed signaling]][phosphainesilide ph 221233	P,C,HS
1E-87 2.1E-87 G A	,	2 \$5.5557	17 2			- 4 - 1	 1.13		4					1 1 1			PALSE	d d Happaleia	1.55		97,P,H
4E-87 2.4E-87 A G	47	12 111 ada@al 1	31 3 ++576455 5.		G 63.4921	101	 21.12		S 2HF74 HH_B		2.45-17 2.45-17		4 INTROM	3 2.10-02 2.10-02		76 1753-494	PALSE	-1 -1 Happaleia	-1.755	8 CO:1002 (regulati bilg://www.auki.alw.aik.gan/raters/diagoniw.s 7625	HS
12-17 2.12-17 C A	27	14 51.1515 aukalilat I	23 4 ++533741 5.		A 15.5212	10	22.18		S SCARF2 HH_1		2.42-42 2.42-42	- 11	11 INTRON	1 2.10-17 2.10-17		46 IV53-25	PALSE	-1 -1 Bagealeia	1.415	1 (1993) [1993] [and adda Mily://an Yan den Cade-Gapla agadesner, (1993)] 31123	HS
15-87 2.15-87 G C		5 50 and a Cital 1	27 2 ++104270 5.		c 56.6743	1155	21.24	299	S POHIZILIP HR_B		2.48-87 2.48-87		I UTR		124		PALSE	-1 -1 Hagealeia	-2.255	8 266657	HS
IE-87 2.1E-87 G A	16	6 17.5 aubalilat I	23 2 ++286978 5.	- SHE G A	A 4.5247	191	1.65		S POMIZILIP HR_B		2.42.47 2.42.47	1	I UTR		574		PALSE	-1 -1 Hagealeia	LIST	266637	P,H,HS
IE-82 2.4E-82 A T	52	15 31.7532 auballitat 8	26 5 ++575179 5.	er SHE A T	T 62.9225	1452	21.25	822	S POPHERLAP MR_B		2.48.47 2.48.47	1	I UTR	1 1 1	1116		PALSE	-1 -1 Ha pratria	-2.855	211137	HS
IE-117 2.1E-17 C T		1 31.3131	15 2 + 232347 5. 24 5 + 111753 5.		T 46.868 8 51.753	1838	36.41	421	S PINKA HH_B S PINKA HH_B		2.12.17 2.12.17	8	25 INTRON	14 2.10-07 2.10-07		24 17516-36 90 17512-12	PALSE	-1 -1 Ha pealeia	-2.10	8 CO:81461 (phenyles http://www.anki.af tensilaty Hetshali http://ww. 5257	HS 55.HS
IE-87 2.1E-87 G A IE-87 2.1E-87 A C		1 10 adallar 1	24 6		A 51.7531 C 63.6733	1446	50.51	40	S PINKA HH_B S PINKA HH_B		2.42.47 2.42.47		CO SA_SITE	12 2.10-07 2.10-07		48 19542-42 67 19541-47	PALSE	-1 -1 He predicts	-1.355	I GosHGC (phanyla kily://www.asti.af lansilafy Halakali kily://www.5237 I GosHGC (phanyla kily://www.asti.af lansilafy Halakali kily://www.5237	
12-87 2.12-87 A C 12-87 2.12-87 C G		75 SEASSE entreliat	11 17 + 171111 5.	CHILD C	G 56,025	1112	56.76	655	S PINKA NH_B	26577	2.42.47 2.42.47	23	25 INTRON	11 2.10.17 2.10.17		62 19511-42 10 1953-45	PALSE	A A Na proleio	-1.85	E CO:HEE phonghe kilp://www.anki.at lensibily Helakeli kilp://w/ 5237 E CO:HEE phonghe kilp://www.anki.at lensibily Helakeli kilp://w/ 5237	0V,HS 55,HS
1E-87 2.1E-87 C G 1E-87 2.1E-87 T C		57 55.7545 establist	13 17 + 178133 5. 24 7 + 232358 5.	- (ME T	G 54.822	1271	55.76	655	S PI4KA HH_B	101 24577	2.46.67 2.46.67		25 SA_SITE	2.10-07 2.10-07	45125		PHLSE	-1 -1 Happalois	-1.55	E COLUME (phoneka kily)//www.anki.at lensibily Matakali kily)//w/ 5237 E COLUME (phoneka kily)//www.anki.at lensibily Matakali kily)//w/ 5237	55,85
1E-17 2.1E-17 T C		47 35.7143 ankalifat	24 11 + 4675 54		C 54.858	425	53.74	753	S SERPINE PIKKASE HH		2.46.47 2.46.47		4 EXON.R	5 2.40-47 2.40-47		12 E.S.SI H H	TOUR	42 I HH_IIII HHET>C HKHSLHALLIPLIT TURH, ;	-2.654	6 GOLDER Johnnyks Miljillun Thranks Complex Organia Miljillur 3833	13
315-17 2.315-17 T C		d 57.5552 aubeführt 1	24 11 ++4625 54	SHET C	C 51.665	2652	8.8	255	S SERPINE PINKASE MM_I	126 26***	2.46-17 2.46-17	21	4 EXON_R	c.16-07 c.16-07	101 1	n 103-33 M H	TRUE	42 I HH_IIII IIIII IIII HABTOC HKASLAALIPLIIT TURH, ; -1 -1 Happaleia	4.92	E COLUME Jakewala kily://au Theanka Campien Organia kily://ar 5853 E COLUME Jakewala kily://aus.auki.al lansilal y Helakali kily://ar 5257	97.85
LIE-17 2.1E-17 C T		8 10 adalah 1	22 4 ++165758 5.		T 66.5242	2113	8.0				2.46-47 2.46-47		23 UTR		31612		PALSE	d d Begrateia	-1.52	I GOUINGI phospin kily://www.anki.al familaly Hylakali kily://wr S237	47,85
		23 72.5 insertion 1				4	61.12		S PINKA MM I		2.15-17 2.15-17		25 UTR		185522	1	PALSE	d d He prairie	1.514	1 69:1160 Jahanda Allet//assemblief Jamilela Heldali Allet//ar 5297	рис
.1E-87 2.1E-87 ACA		1 2.01 investion 1	1,10,102,114 0.	alaa i	aca1	4	2.0				2.45.42 2.45.42		23 UTB		105611		PALSE	d d Hageabria	-1.201	1 GO(IH41) jakanaka kilaj//uwu.eski.el lessilela Melakeli kilaj//uvi 5237	P.85
		1 III establist	21 5 ++155854 54		A 48.5572	4915	41.53				2.10-17 2.10-17	55	SS EXON.R	1 2.10-17 2.10-17		9 E.I.S C C	TRUE	THE I HH IST INGON MANAPAROGOOG VAR SE HI-		I 99:0000 Jahanaka Milet//augumaki.el Janiilelle Melaheli Milet//ar 5237	5
2.12.87 2.12.87 ACA 2.12.87 2.12.87 CAT 2.12.87 2.12.87 G A	,													11 2.15-17 2.15-17		75 17513-37	PALSE	1 1 Haraki			
.1E-87 2.1E-87 CAT .1E-87 2.1E-87 G A	1	11 111 establish	11 5 ++171275 54	-SHEC G	G 31.3535	2172 1	\$1.35	581	S AIPHS HH 4		2.10-12 2.10-12		20 INTROM							I SQ:IIII industries of announced lastication of exercise anticide laster (S1213	
2.1E-87 2.1E-87 CAT	1 11 23		11 5 ++171276 5. 24 7 ++171277 5.		G 58.5656 A 56.7554	2172	51.55 57.63		S AIPHS HH_S S AIPHS HH_S		2.42.47 2.42.47	21	28 INTRON.	14 2.12-17 2.12-17		IS 17514-53	PALSE	d d Happalois	-1.10	I COLUME (industries of applicite) and action of support adjusting by an ASI203 I COLUME (industries of applicite) (adjustication of support adjusting by an ASI203	HS
1.18-87 2.18-87 CAT 1.18-87 2.18-87 G A 1.18-87 2.18-87 C G	1 11 25	11 10 aufa03al 1	24 7	SHEC A				665 346	S AIPHS HH_1 S AIPHS HH_1	1447 16252 1447 16252	2.42-12 2.42-12 -	21 21 21		14 2.1E-87 2.1E-87 15 2.1E-87 2.1E-87	105 1	15 1V514-55 16 1V515-28			-1.12		HS
.45-87 2.45-87 CAT .45-87 2.45-87 G A .45-87 2.45-87 G G .45-87 2.45-87 G A	1 11 12 11 12	11 100 antalian 1 25 32 antalian 1	24 7 ++178277 5.	SHEC A	A 35.7554	1534	\$2.65	565 346 747	S AIPHS HH_1 S AIPHS HH_1 S L2TR1 HH_8	1447 16252 1447 16252 1467 16252	2.45-17 2.45-17	20 20 20 20 20 20 20 20 20 20 20 20 20 2	28 INTRON	18 2.10-07 2.10-07	43 135 1 23 27	IS 17514-55	PALSE	A A Happaleia		1 CO:1111 [industries of applicate] [articulies of ecopers called a by at 151215	HS HS HS

Comprehensive, interactive and visual tools are required to efficiently and correctly interpret an experiment

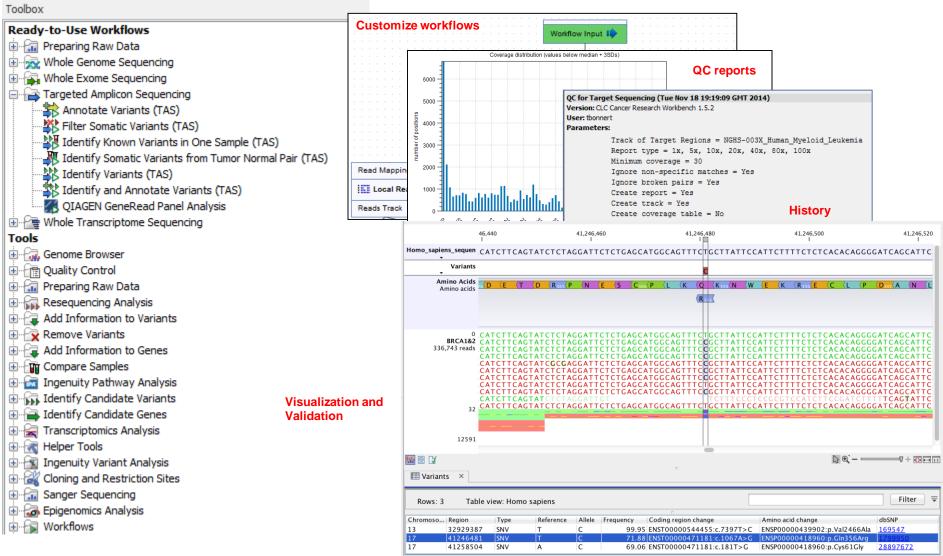


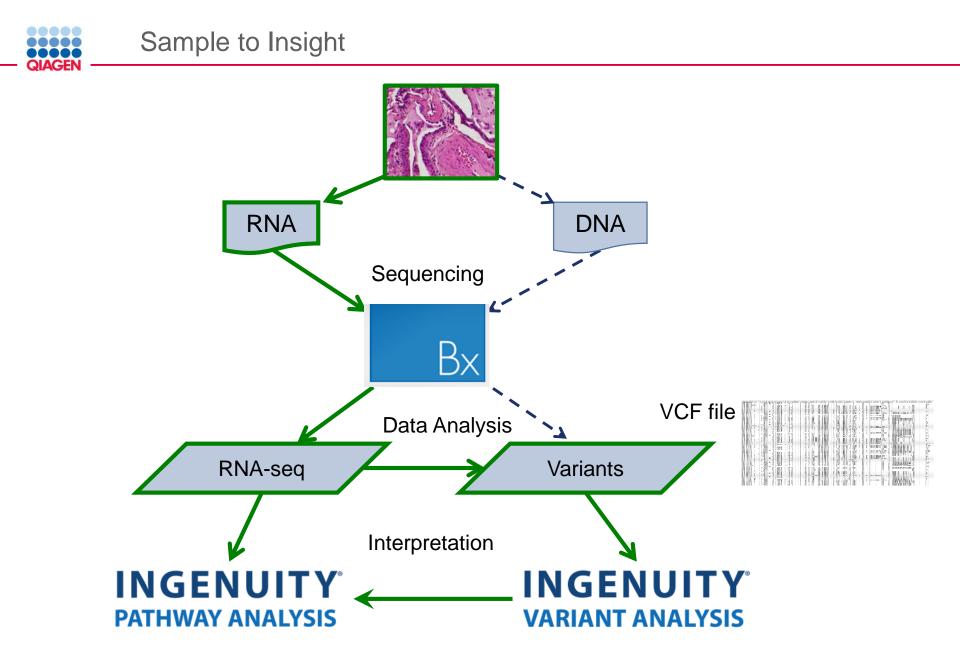
Ingenuity Variant Analysis Workflow





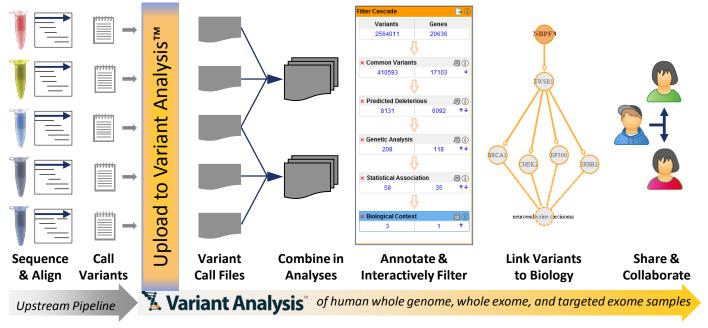
Streamlined workflows and a rich toolbox to efficiently process data



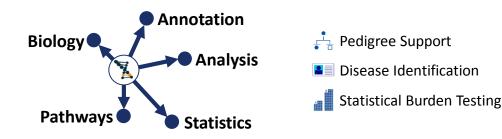




Ingenuity Variant Analysis

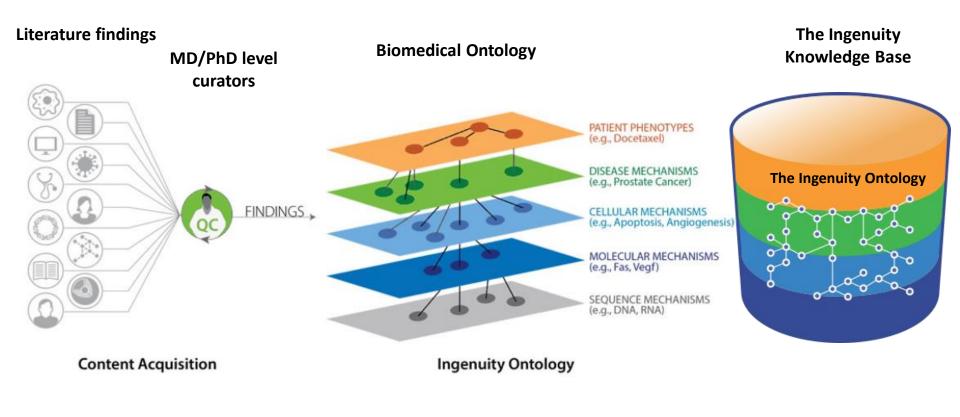


- Stratification Studies 🗸
- Large Cancer Studies 🗸
- Genetic Disease Cohort 🗸
 - Trio/Quad Study 🗸
 - Tumour-Normal Pair 🗸
 - Personal Genome 🗸





Unprecedented Access to Literature Knowledge

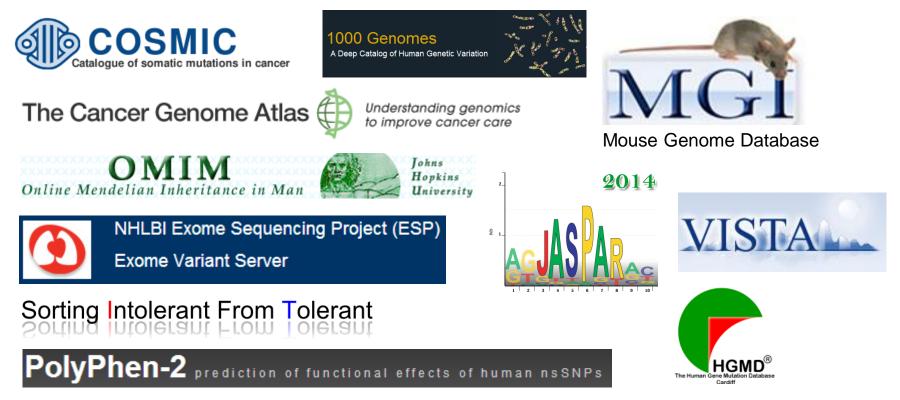






Variant Analysis Content

Quality, Context, Coverage, and Timeliness of Content (ca.1/2014)



Additionally

- 349,748+ Ph.D./M.D. expert-curated human phenotype-associated mutation findings
- ~3M+ manual literature findings
- 21,458+ curated disease models
- 185,310+ curated pharmacogenetic (PGx) findings

<u>Title,</u> Locati on.



www.allelefrequencycommunity.org

- Leverage the world's largest pool of anonymized allele frequency data
- Reduces false positives in analyses by removing variants that are commonly seen in the general population
- Contains Whole Exome AND Whole Genome data
- Better representation of Insertions and Deletions

Larger than ANY other public resource

- □ AFC launched with 70,000 samples with >8,000 as whole genomes
- □ 12x larger than Exome Variant Server data
- The initial launch version of the database already provides a 43% average false positive rate reduction in a benchmarking set of whole-genome Diagnostic Odyssey cases
- AFC will grow as more people opt-in
 - Launched on 25th February 2015 with 70,000 Samples including 8,000 Whole Genomes
 - Currently at over 100,000 samples, including over 14,000 Whole Genome samples

Sample to Insight



Use biological associations and molecular interactions

Filter	×		Re	egulators of…
Biological Context				
Keep only 💌 variants		Pathways		
🗹 within 2 hops 💌 upstream				
that are known or predicted to				
Affect 💌				
genes listed below or genes implicated in the following of processes, pathways, phenotypes, domains, activities, or			Disease	
Enter and select term		Variants		
Diseases / Phenotypes / Genes / Signalling p Biological processes / Protein domains / Protei				,
Upload gene list file(s)				
and genes within 1 hop 🔽 downstream of above				
include diseases consistent with the phenotypes above	Ve Your		otein	ILIIRA
Apply		st do	omain	
			JAKI	JAK2 MMP TAT3 GFB
Findings (55 citations)			×	$\prec \mid \Lambda / \mid$
	apert syndrome: identification of the first part	ial gene deletion, and an Alu	A	
element insertion from a new sub				FGFRI
	ermline mutant human FGFR2 protein (p.P253R) is	observed with autosomal domin	ant fo	GFR3 FGFR2 TWIST
Apert's syndrome in human (St Gain-of-function heterozygous g	uay size: multiple individuals). ermline mutant human FGFR2 protein (p.S252W) is	observed with autosomal domin		\prec \vee Υ
Apert's syndrome in human (St			▼	
				craniosynostosis

Sample to Insight



Case Study: Pheochromocytoma (PCC)



Hereditary pheochromocytoma (PCC) is a neuroendocrine tumor of the medulla of the adrenal glands

Whole exome sequencing (Agilent SureSelect) on Illumina Genome Analyzer II

Sequence data obtained from European Nucleotide Archive (ENA)

http://www.ebi.ac.uk/ena/data/view/ERR031607-ERR031626

Published in Nature Genetics (2011); PMID: 2168591

 Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma

Barcode	Display Name	State	^{i∲} Subject	Variants	
ERS025965	924_Hereditary_Pheochromocytoma	case	924	231460	Independent hereditary
ERS025967	3037_Hereditary_Pheochromocytoma	case	3037	283434	pheochromocytoma
ERS025973	3121_Hereditary_Pheochromocytoma	case	3121	243291	
ERS025971	NA11881_Control	control	NA11881	731542	■
ERS025969	NA12144_Control	control	NA12144	304008	
ERS025974	NA12892_Control	control	NA12892	681906	Independent
ERS025970	NA12813_Control	control	NA12813	548289	НарМар
ERS025966	NA12763_Control	control	NA12763	1098602	samples
ERS025968	NA12761_Control	control	NA12761	834283	
ERS025972	NA12750_Control	control	NA12750	488217	



LETTERS



Exome sequencing identifies *MAX* mutations as a cause of hereditary pheochromocytoma

Iñaki Comino-Méndez^{1,2,15}, Francisco J Gracia-Aznárez^{2,3,15}, Francesca Schiavi^{4,15}, Iñigo Landa¹, Luis J Leandro-García¹, Rocío Letón¹, Emiliano Honrado⁵, Rocío Ramos-Medina⁶, Daniela Caronia⁷, Guillermo Pita⁷, Álvaro Gómez-Graña¹, Aguirre A de Cubas¹, Lucía Inglada-Pérez^{1,2}, Agnieszka Maliszewska¹, Elisa Taschin⁴, Sara Bobisse⁴, Giuseppe Pica⁸, Paola Loli⁹, Rafael Hernández-Lavado¹⁰, José A Díaz¹¹, Mercedes Gómez-Morales¹², Anna González-Neira⁷, Giovanna Roncador⁶, Cristina Rodríguez-Antona^{1,2}, Javier Benítez^{2,3}, Massimo Mannelli¹³, Giuseppe Opocher^{4,14}, Mercedes Robledo^{1,2} & Alberto Cascón^{1,2}



Examples

- Tumor vs Normal
- Trio (Hereditary)
- Stratification (affected vs unaffected)



Live Demo

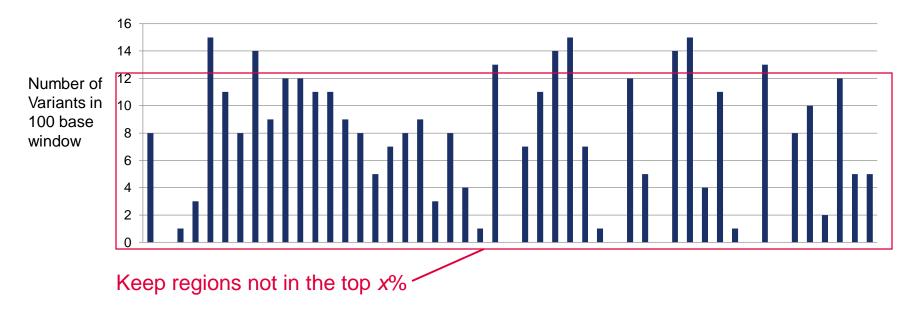


SLIDE EXPLAINING NOISE FILTER





SLIDE EXPLAINING NOISE FILTER



Will ignore top x% most exonically variable 100 base regions



Identification and Removal of Artifacts

Counts based on single sample, qual 20, allele frequency < 3%

	A	В
1	Gene Symbol	Count
_	MUC4	129
	PTPRN2	98
4	MUC6	95
5	HLA-DRB1	89
6	MUC16	80
7	PRSS1/PRSS3	63
8	CSF2RA	60
9	PDE4DIP	53
10	BAGE3; BAGE4; BAGE2	53
11	PRIM2	48
12	MAP2K3	46
13	KCNJ12; KCNJ18	45
14	C9orf96	44
15	CDK11A/CDK11B	43
16	MUC12	40
17	AQP7	40
18	TUBGCP2	39
19	CDH4	39
20	HLA-DRB5	39
21	SLC22A2	39
22	C7orf50	36
23	ANKRD36B (includes others)	34
24	PRKAG2	32
25	TTC34	31
26	OR8U1	31
27	EPHA8	29
28	FRG2 (includes others)	29
29	SORCS2	29
30	COL5A1	29

1.1	J	К	L	М	N	0
		Pct of	Cumulative		Cumulative	Cumulative
Variants	Count of	Genes in	Pct of		Sum of	Pct of
per Gene	Genes	Analysis	Genes		Variants	Variants
1	3795	56.68%	56.68%		3795	23.40%
2	1307	19.52%	76.21%		6409	39.51%
3	602	8.99%	85.20%		8215	50.64%
4	322	4.81%	90.01%		9503	58.58%
5	194	2.90%	92.91%		10473	64.56%
6	114	1.70%	94.61%		11157	68.78%
7	88	1.31%	95.92%		11773	72.58%
8	48	0.72%	96.64%		12157	74.95%
9	32	0.48%	97.12%		12445	76.72%
10	28	0.42%	97.54%		12725	78.45%
11	32	0.48%	98.01%		13077	80.62%
12	16	0.24%	98.25%		13269	81.80%
13	13	0.19%	98.45%		13438	82.84%
14	15	0.22%	98.67%		13648	84.14%
15	13	0.19%	98.86%		13843	85.34%
16	11	0.16%	99.03%		14019	86.43%
17	7	0.10%	99.13%		14138	87.16%
18	5	0.07%	99.21%		14228	87.71%
19	3	0.04%	99.25%		14285	88.06%
20	6	0.09%	99.34%		14405	88.80%
21	1	0.01%	99.36%		14426	88.93%
22	2	0.03%	99.39%		14470	89.21%
23	2	0.03%	99.42%		14516	89.49%
24	7	0.10%	99.52%		14684	90.52%

For example, if set at 5%:

Keep genes that are not in the top 5% most exonically variable

> Will ignore the top 5% most exonically variable genes

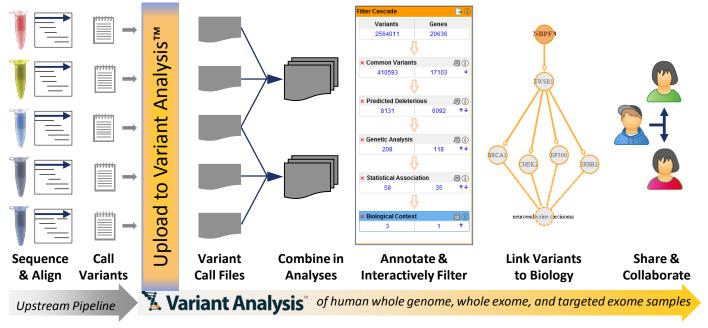


Summary

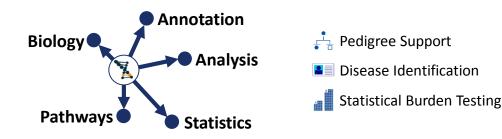
- Sample to Insight



Ingenuity Variant Analysis



- Stratification Studies 🗸
- Large Cancer Studies 🗸
- Genetic Disease Cohort 🗸
 - Trio/Quad Study 🗸
 - Tumour-Normal Pair 🗸
 - Personal Genome 🗸





ly Samples My Ana	lyses Put	Dications	Claud	in ProbVar [×]		lter			×
Filter Cascade		- (1)	Summ	nary Variants	Gene	Confidence			Rename
Variants	Genes				Export	Keep only 👻 variants which satisfy all of the	se criteria:		
46076	9648		Chr.	Position	Gene				
- Û			6	31236668	3'UT	Call quality is at least 20 in any cas	e or at least 20 📩 in any	y control	
× Confidence	(J I	6	31236767		Variant passed upstream pipeline filtering	AND		
46076	9648		6	31236800	3'UT		AND		
Û			6	31236821	3'UT	Read depth is at least 10	mple		
× Common Variants		9 1	6	31236853	3'UT		AND		
16809	5996	++	6	31236862	3'UT	Allele fraction is at least 5 * % in any			
Ϋ́			6	31237773	Exor		AND		
× Predicted Deleteri	ous	9 (1)	6	31238027	Exor	Outside top 0.2	Ily variable 100base windows in AND	healthy public genomes	
5583	3474	→ ↓	6	31238909	Exor	Outside top 1 * % most exonica	Ily variable genes in healthy pul	hlic genomes (1000 Genomes	.)
л			6	31238931	Exor		iny variable genes in nearing par		·)
V			6	31238995	Exor	Subsequent filters only treat a variant as present	for samples that also satisfy the	e Keep criteria.	
× Genetic Analysis 38	5		6	31239050	Exor		Apply		
30	5		6	31239100	Exor	p.51251, p.112		In-Itame, sync	
₩ 🗸		_	6	31239101	Exor	HLA-C p.S123F, p.Y12	23	missense	Tolera
× Biological Contex	t		6	31239501	Exor	HLA-C p.A73E		missense	Dama
38 Recalculate wh	5 on filtors ch		8	11700213	3'UT	CTSB			
		lange	8	11700373	3'UT	CTSB			
egend [show]			8	11700676	RUIT	CTSB			



My Samples My A	nalyses P	ublications	Claudin ProbVar [x]	ack
Filter Cascade		-	Summary Variants Genes Groups/Complexes Pathways Processes Diseases Overview Share Publi	ish
Variants	Genes		Filter	×
46076	9648		Common Variants	ename
<u>ا</u>	ን			
× Confidence 46076	9648	 ()	Exclude variants that are observed in any of these populations with an allele frequency of	
40070	} }		✓ at least ▼ 3 [★] % in the 1000 Genomes Project	
× Common Variar	its	Ø ()	at least 💌 3 📥 % in the ExAC	
16809	5996		✓ at least ▼ 3 ★ % of all	
× Predicted Delet	erious 3474	月 () ↑↓	at least 🔹 3 👘 % in the Allele Frequency Community (includes ExAC and CG)
4	} }			
× Genetic Analys		Ø ()	OR	
38	5		are present in dbSNP	
× Biological Cont 38	5	Change	* The public Complete Genomics genomes are included in the AFC	
Add	d Filter		Apply	
Legend [show]				



ly Samples My Ai	nalyses Publications	Claudi	n ProbVar [×]			0	
ilter Cascade	Ū 🖨	Summ	n <mark>ary</mark> ⊨ Variants	Gene	es Groups/Complexes Pathways Processes Diseases Overview	nare	
Variants	Genes	Edit		Expo		_	
46076	9648				Predicted Deleterious	Rer	
J	1	Chr	Position	Gei	Keep only variants that	pact	SIFT F
\		6	31236668	3'L	are experimentally observed to be associated with a phenotype:		
Confidence	 (1)	6	31236767	3'L	Disease-associated according to computed ACMG Guidelines classification		
46076	9648 🔸	6	31236800	3'U	✓ Pathogenic		
J	ι Ι	6	31236821	3'L	✓ Likely Pathogenic Uncertain Significance		
\					Likely Benign		
× Common Varian	nts 🗐 🛈	6	31236853	3'U	Benign		
16809	5996 ++	6	31236862	3'L	Listed in HGMD®		
J	ι _	6	31237773	Ex	OR		Activa
`		6	31238027		are associated with gain of function of a gene		Dama
Predicted Delete		6	31238909	Ex	Gene Fusion		
5583	3474				Gene Fusion Inferred activating mutation by Ingenuity		
1	ι Ι	6	31238931	Ex	Predicted gain of function by BSIFT		
	-	6	31238995	Ex	Copy Number Gain		
× Genetic Analysi	\sim	6	31239050	Ex			Activa
38	5 ++	6	31239100	Ex	are associated with loss of function of a gene	onyme	Activa
- 1	ι Ι				Frameshift, in-frame indel, or start/stop codon change	orryrrie	
		6	31239101	Ex	Missense unless predicted tolerated by SIFT or PolyPhen-2		Tolera
K Biological Conte	~~ _	6	31239501	Ex	Nullizygous ✓ Splice site loss up to 2 ★ bases into intron or as predicted by MaxEntScan		Dama
38	5 ↑ ▼ when filters change	8	11700213	3'L	Opine site loss up to 2 Jases into inition of as predicted by MaxEntocan		
	d Filter	8	11700373	3'L	Apply		
Add		8	11700676	311			
egend [show]							



My Samples My Analyses Publications	Claudin Prob	Var [×]	(i) Feedback
Filter Cascade 📑 (j)	Summary \	/ariants Genes Groups/Complexes Pathways Processes	Diseases Overview Share Publish
Variants Genes	Edit Colum	Filter	×
46076 9648	Chr Posi	Genetic Analysis	Rename
1 Û	6 312	Use recommended settings for: (Custom) Tumor-specific va	riants Set
× Confidence	6 312	Pair/match samples from the same individual	
46076 9648 +	6 312	Restrict to transmitted variants	
Ŷ	6 312	Case Samples	Control Samples
× Common Variants	6 312	Keep only variants which are	Exclude variants which are
16809 5996 ++	6 312	associated with gain of function	✓ associated with gain of function
Ĵ.	6 312	To control specific gain of function types, use the Predicted Deleterious filter	To control specific gain of function types, use the Predicted Deleterious filter
	6 312	OR	A OR
× Predicted Deleterious	6 312	Homozygous Het-ambiguous	N Homozygous Het-ambiguous
	6 312	Compound Heterozygous S Veterozygous A Heterozygous	D Compound Heterozygous <a> ✓ Heterozygous ✓ Haploinsufficient
	6 <u>3</u> 12	Hemizygous	✓ Hemizygous
× Genetic Analysis	6 312	AND	AND
38 5	6 312	the genotypes selected above occur in at least	the genotypes selected above occur in at least
U 🗘 🗌	6 312	2 * of the 5 case samples (40%) at gene level *	1 of the 5 control samples (20%) at variant level
× Biological Context	6 312		
38 5 ↑ ▼ Recalculate when filters change	8 117		Apply
Add Filter	8 117		
Legend [show]	8 1170	00676 SUITE CTSB	

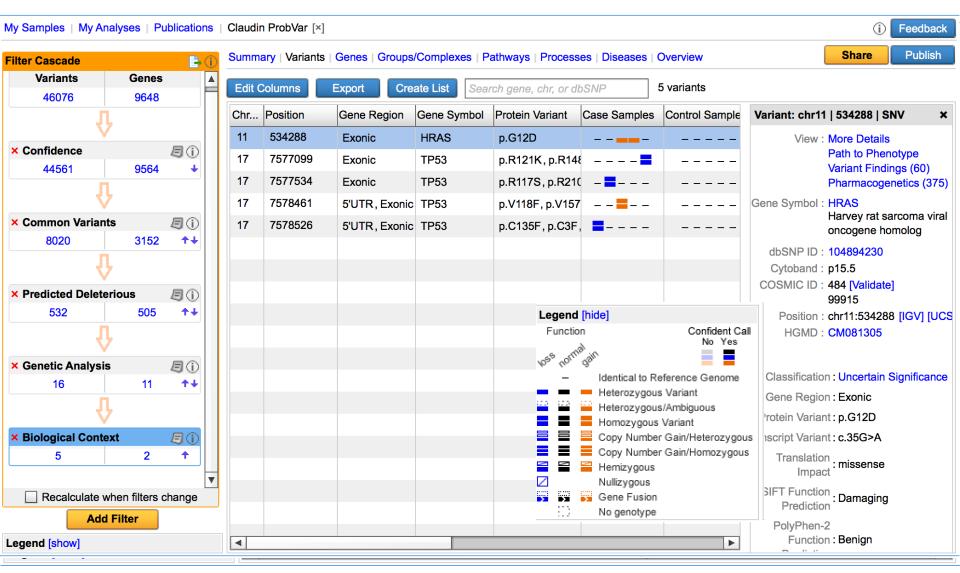


My Samples My Analyse	es Pu	Iblications	Claud	lin Pro	bVar [×]	① Fe	edback
Filter Cascade		- (j	Sum	nary	Variants Genes Groups/Complexes Pathways Processes Diseases Overview	Share	Publish
	Genes		Edit	Colur	Filter		×
46076	9648		Chr.	Pos	Biological Context		Rename
× Confidence			6	31;	Keep only variants		
46076	9648	月()	6	312	Keep only variants		
46076	9648		6	311 311	within 1 hop vpstream	Genes	
× Common Variants		月 (1)	6	312	that are known or predicted to	3,3'-diindolylmethane ABL1 AGT	
16809	5996	+ +	6	31;	Affect	AKT1 AKT2	
Ŷ			6	31	genes listed below or genes implicated in the following diseases,	AKT3 ALX1 AMELX	
× Predicted Deleterious	S	Ø ()	6	31:	processes, pathways, phenotypes, domains, activities, or biomarkers	ARHGAP21	
5583	3474	+ +	6	31:	Enter and select term	beta-estradiol BMI1	
Ŷ			6	312 312	× epithelial-mesenchymal transition [process]	BMP2 BMP7 bosutinib	
× Genetic Analysis						C1orf61 CAV1	
38	5	++	6	31; 31;		CD44 CDC42 CDH1	
- U			6	312		CDH1 CDH11 CLIC4	
× Biological Context		Ø () -	0	>1		v	
38	5		8	117	Upload gene list file(s)		
Recalculate when		nange	8	117	and genes within 1 hop - downstream of above		
Legend [show]			8	117	include diseases consistent with the phenotypes above		
					Apply		

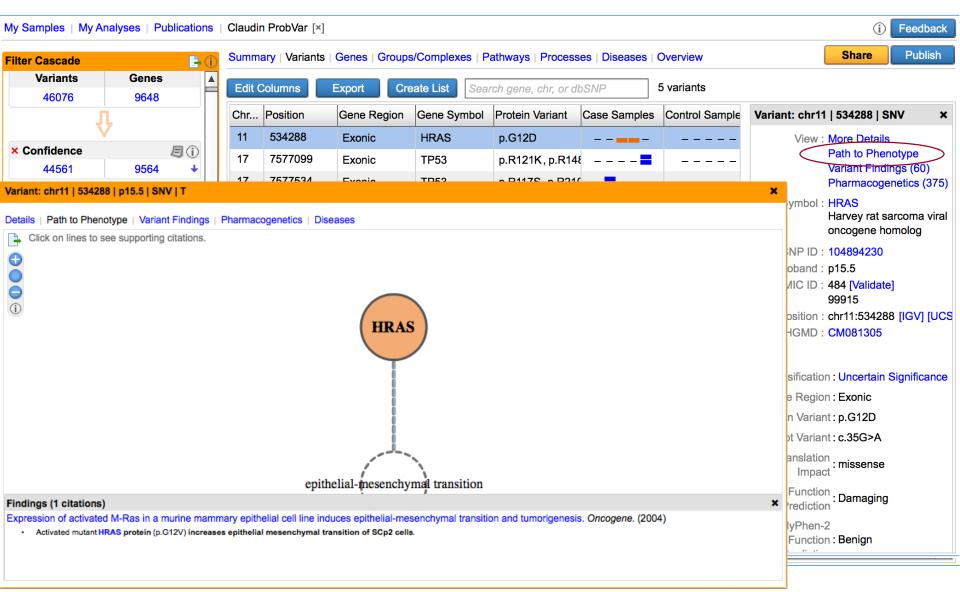


My Samples My Analyses Public	ations C	Claudin ProbVar [×]	Filter ×	dback	Ĵ
Filter Cascade	B ① S	Summary Variants	Cancer Driver Variants Rename	blish	Ì
Variants Genes				i –	
46076 9648		Biolog	Keep only variants that are found in	ns	
	-	Cance	Cancer-associated mouse knockout phenotypes View list of phenotypes	ssi Pol	
× Confidence	11		Cancer-associated cellular processes with appropriate directionality	22	
44561 9564	+	Comm	View list of processes		
		Genfic	Cancer-associated pathways with appropriate directionality View list of pathways	ss ss	
	11	Custo	Cancer therapeutic targets	Po	
8020 3152 1	++	9	View list of drug targets	Pr	
L Û		Genet	✓ Published cancer literature variant level	Be	
	1	Pharm	Known or predicted cancer subnetwork regulatory sites View list of disease genes	Pr	
532 505	*+	Physic	COSMIC at a frequency greater than or equal to 💌 0.1 📥 %	Pr	
U 4		1.	✓ TCGA at a frequency greater than or equal to ▼ 0.1 ↑ %	Pr	
× Genetic Analysis	0	1 Predic		Po	
	++	Statis		Pr	
, ,		Julia	Involved in any of the diseases listed below	Po	
V	_	User-I	▼		
× Biological Context	11	M 15200	× Breast Cancer		
5 2 4	⁺_ /	M 15452		J	
	▼/	IN IOTOL	Apply		
Recalculate when filters chan	ge	L. L			
Add Filter	ノ				
Legend [show]		•			





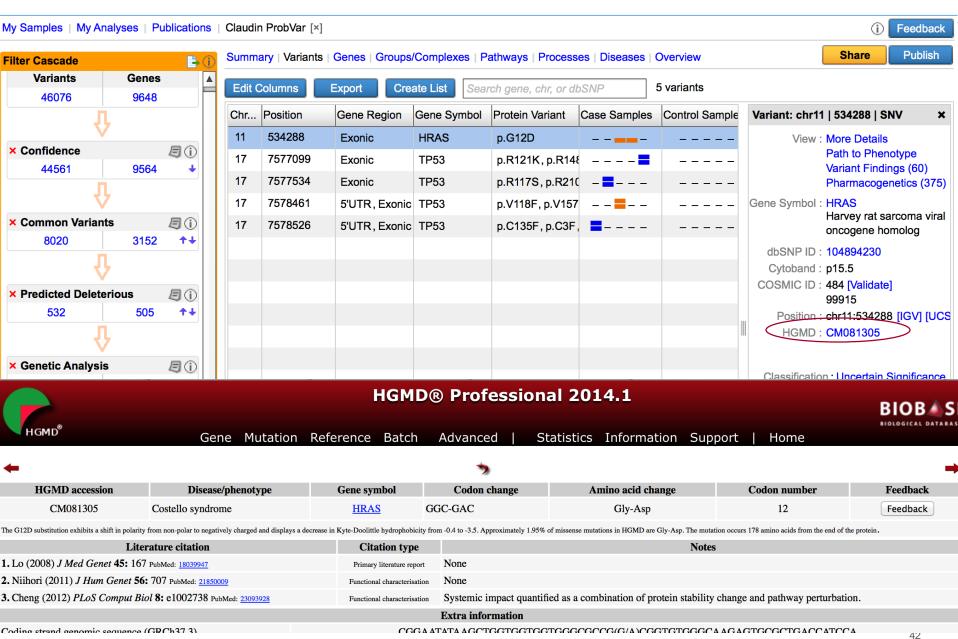




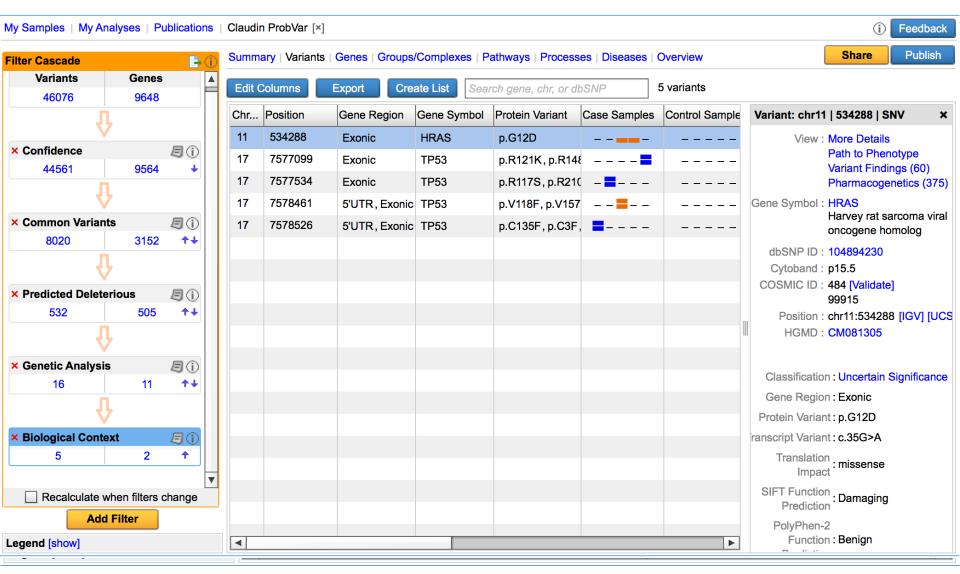


My Samples My Analyses Publications Claudin ProbVar [x]								Feedback
Filter Cascade Summary Variants Genes Groups/Complexes Pathways Processes Diseases Overview								Share Publish
Variants Genes	Edit Columns E	xport Create	e List Sear	ch gene, chr, or dl	bSNP	5 variants		
46076 9648								
л	Chr Position	Gene Region Ge	ene Symbol	Protein Variant	Case Samples	Control Sample	Vari	ant: chr11 534288 SNV ×
	11 534288	Exonic H	IRAS	p.G12D				View : More Details
× Confidence / [] (i)	17 7577099	Exonic T	P53	p.R121K, p.R148				Path to Phenotype
44561 9564 🔸	17 7577534	Exonio T	D53	n P1176 n P210				Variant Findings (60)
Variant: chr11 534288 p15.5 SNV T								Pharmacogenetics (375)
Dataile - Bath to Dhanatana - Mariant Findiana - Dhanasanatina - Dianasan								Symbol : HRAS Harvey rat sarcoma viral
Details Path to Phenotype Variant Findings Pharmacogenetics Diseases								oncogene homolog
Findings (40 citations) The Exomes of the NCI-60 Panel: A Genomic Resource for Cancer Biology and Systems Pharmacology. Cancer Res. (2013)								SNP ID : 104894230
							ytoband:p15.5	
Somatic missense heterozygous mutant human HRAS gene (c.35G>A translating to p.G12D) is associated with carcinoma in human breast (observed in 1 of 1 samples).							SMIC ID : 484 [Validate]	
Frequent Mutation of the PI3K Pathway in Head and Neck Cancer Defines Predictive Biomarkers. Cancer Discov. (2013)								99915
Somatic missense mutant human HRAS gene (c.35G>A translating to p.G12D) is associated with squamous-cell carcinoma in human head and neck (observed in 2 of 7 samples).								Position : chr11:534288 [IGV] [UCS
 Somatic missense mutant human HRAS gene (c.35G>A translating to p.G12D) is associated with squamous-cell carcinoma in human head and neck (observed in 2 of 7 samples). 								HGMD : CM081305
RAS Mutations Are Associated With the Development of Cutaneous Squamous Cell Tumors in Patients Treated With RAF Inhibitors. J Clin Oncol. (2012)								
Somatic missense mutant human HRAS gene (c.35G>A translating to p.G12D) is associated with keratoacanthoma in skin from human chest (observed in 1 of 1 samples).								assification : Uncertain Significance
RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med. (2012)								ne Region : Exonic
Somatic missense mutant human HRAS gene (c.35G>A translating to p.G12D) is associated with keratoacanthoma in skin from human leg (observed in 1 of 4 samples).								ein Variant : p.G12D
 Somatic missense mutant human HRAS gene (c.35G>A translating to p.G12D) is associated with keratoacanthoma in skin from human torso (observed in 1 of 7 samples). 								ript Variant : c.35G>A
Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. Nat Genet. (2012)								
Mutant human HRAS gene (c.35G>A) is associated with nevus sebaceous in human.							Translation Impact	
 HRAS mutants identified in Costello syndrome patients can induce cellular senescence: possible implications for the pathogenesis of Costello syndrome. J Hum Genet. (2011) Change of function heterozygous germline mutant human HRAS protein (p.G12D, alternately c.35G>A) is observed with childhood-onset Costello syndrome in human (unknown geographic location). 							impolot	
							T Function : Damaging Prediction	
i constanti,								PolyPhen-2
Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder. Nat Genet. (2011) Somatic missense mutant human HRAS gene (c.35G>A translating to p.G12D) is associated with carcinoma in human urinary bladder (observed in 2 of 11 samples).								Function : Benign
 Somatic missense mutant human HRAS gene (c. Somatic missense mutant human HRAS gene (c. 						R 0.0		
						V		







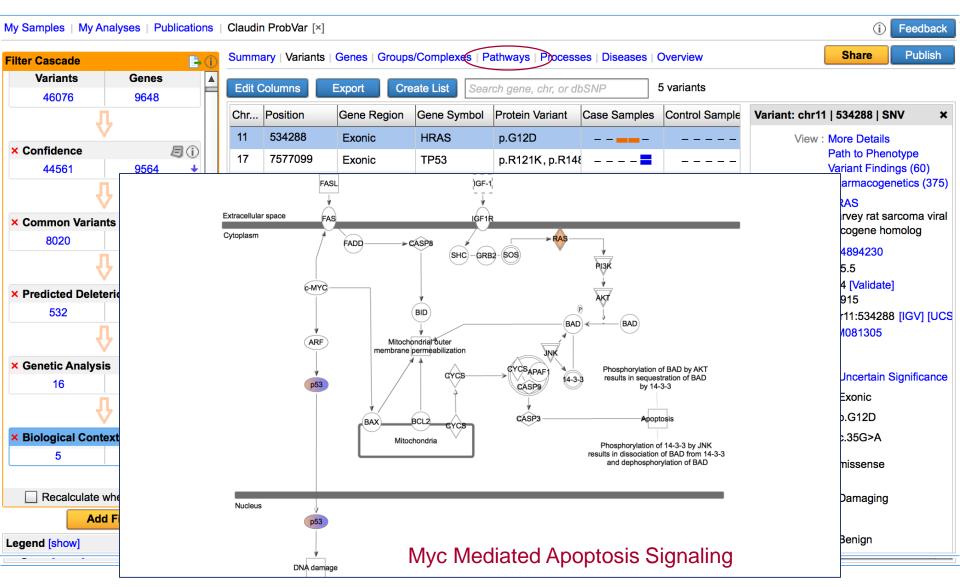




Samples My Analy	ses Pu	blication	IS	Claudin	ProbVar [×]							() Feedb
ter Cascade		-	\odot	Summa	<mark>ry</mark> ∣ Variar	its Genes	Groups	/Complexes	athway	ys Process	ses Diseases	Overview	Share Publi
Variants	Genes			Edit C	olumns	Export	Cre	ate List	aarah gar	ne, chr, or dl	hend	5 variants	
46076	9648					(i			1]		
۰. Ū					Position		Region	Gene Symb			Case Samples	Control Sample	Variant: chr11 534288 SNV
¥				11	534288	Exoni	1	HRAS	p.G1	2D s +∯%Contro			View : More Details Path to Phenotype
Name					▲ #Genes						ols -		Variant Findings (60)
Mdm2-Tp53-ubiquitin				680E-4	1	4	4	80	0	0			Pharmacogenetics (
Mdm2-Tp53-Mdm4				520E-4	1	4	4	80	0	0			Gene Symbol : HRAS Harvey rat sarcoma
lkB-Tp53				200E-4	1	4	4	80	0	0			oncogene homolog
Ras				039E-4	1	1	2	40	0	0			dbSNP ID : 104894230
Hd-neuronal intranucl	ear inclus	sions	1.2	260E-3	1	4	4	80	0	0			Cytoband : p15.5
Predicted Deleterio	us	Ø ()											COSMIC ID : 484 [Validate] 99915
532	505	++											Position : chr11:534288 [IGV]
Л													HGMD : CM081305
V													
Genetic Analysis	11	月 ① ★↓											Classification : Uncertain Significa
0													Gene Region : Exonic
₩.													Protein Variant : p.G12D
Biological Context		Ø (1)											ranscript Variant : c.35G>A
5	2	+	•										Translation Impact
Recalculate when			•										SIFT Function : Damaging Prediction
Add Fil	ter												PolyPhen-2
gend [show]				•							1	•	Function : Benign



Results: The Short List





Results: The Short List

My Samples My Analyses Publications Claudin ProbVar [x]															
Filter Cascade		₽ 0	Summa	Summary Variants Genes Groups/Complexes Pathways Processes Diseases Overview Share Publish											
Variants	Genes	A	Edit C	Columns	Export Cre	ate List Sear	ch aene	chr or dh	SNF	>	5 variants				
46076 9648															
				Position	Gene Region	Gene Symbol	Protein V	/ariant	Case	e Samples	Control S	ample	Variant: chr	11 534288	SNV ×
		11	534288	Exonic	HRAS p.G12D						View : More Details				
× Confidence			17	7577099 Exonic		TP53	p.R121	p.R121K, p.R148		=			Path to Phenotype Variant Findings (6		
44301	9304		17	7577534	Exonic	TP53	p.R1175	6, p.R210	_						genetics (375)
V				Name				p-value		#Genes	#Variants	#Cases	%Cases	#Controls	%Controls
× Common Varia		9 ()	17	arrest in G1	/S phase transi	tion of embryon	ic cell lin	1.058E-	-8	2	5	5	100	0	0
8020	3152	++		arrest in dev	velopmental pro	cess of kidney	cell lines	3.528E-	-8	2	5	5	100	0	0
•				arrest in gro	wth of kidney c	cell lines		3.528E-	-8	2	5	5	100	0	0
× Predicted Deleterious				arrest in G1/S phase transition of fibroblasts 5.292E-8 2 5 5							5	100	0	0	
532	505	<u>++</u>			arrest in G1/S phase transition of connective					2	5	5	100	0	0
L L				G1/S phase transition of embryonic cell lines							-			-	-
× Genetic Analy	¥ eie	J ()				•		7.409E-		2	5	5	100	0	0
16	11	4 ↓		arrest in cell	cycle progress	ion of breast ce	ell lines	9.878E	-8	2	5	5	100	0	0
				senescence of epidermal cells 9.878E-8 2 5 5						5	100	0	0		
	<u>V</u>			senescence of dermal cells 1.588E-7 2 5 5							5	100	0	0	
× Biological Context 🛛 🗐 🕕				cytostasis of epidermal cells				1.588E-	-7	2	5	5	100	0	0
5 2 +				cytostasis o	cytostasis of dermal cells 1.588E-7 2				2	5	5	100	0	0	
	e when filters c	▼ hange											SIFT Funct Predict	^{ion} : Damagin ion	ıg
									_				PolyPher Funct	n-2 ion : Benign	
Legend [show]													5		



Ingenuity Variant Analysis

- Easy to use, allows scientific iteration
 - □ Filter variants, real-time, based on both standard and proprietary criteria
- Provides variant filtering using public and proprietary databases
 Allele Frequency Community
- Powerful tools for genetic and statistical tests
- Relate variants to literature and biology
 - Narrow-down, discover, and prioritize variants based on literature findings, pathway and biological associations
- Integrate variants with GWAS, gene expression, or other gene or positional data using BED files





Thank You!!

Dev Mistry, Ph.D. Field Applications Scientist Devendra.Mistry@qiagen.com

Sample to Insight



OTHER SLIDES

- Sample to Insight



Increase application performance by pre-filtering large samples sets

Cases and Controls 2 Focus the Analysis 3 Sample-specific options Analyze X	
Considerations for whole-genome analysis Please review these pre-filtering options.	Remove unnecessary low quality or low value
To make the size of the analysis you are creating manageable, Ingenuity recommends selecting at least one of these pre- filtering options. Pre-filtering will remove the least scientifically useful data so you can focus your analysis on regions of greater interest.	variants upfront to improve analysis
Keep only variants in Exonic regions ①	speed
Exclude common variants that are observed with high allele frequency in public databases show details	
Keep only variants above minimum confidence standards show details	
Back Next	



Reduce false positives with inclusion of the ExAC database for filtering out common variants

Filter	×
Common Variants	
Exclude variants that are observed in any of these populations with an allele frequency of	
✓ at least ▼ 3 ★% in the 1000 Genomes Project	
☑ at least 💌 3 📥 % in the ExAC	
✓ at least ▼ 3 ★ % of all ▼ NHLBI ESP exomes	
✓ at least ▼ 3 ★% in the Allele Frequency Community (includes ExAC and CGI)	
OR	
are present in dbSNP	
* The public Complete Genomics genomes are included in the AFC	•
Apply	

 The Exome Aggregation Consortium (ExAC)

•

- Exome sequencing data from a wide variety of large-scale sequencing projects
- Spans 60,706 unrelated individuals sequenced as part of various disease-specific and population genetic studies.



Faster Variant Analysis setup by grouping control samples into defined libraries

Welcome F	Rupert Yip Logo	ut What's new?		Help						
lanage M	y Samples My /	Analyses Publications	My Control Libraries							
Upload	Refresh	Share Analyze	Annotate New Library							
Showing 8	2 samples									
ID	Barcode	Display Name	Description							
267681	PGP161	PGP161	myopia dataset							
408034	LP6005636-	LP6005636-DNA_F02	LP6005636-DNA_F02							
358322	Reportability	Reportability_tests		Cases and Controls						>
267685	PGP84	PGP84	myopia dataset	Select and drag samples	to docianato	caso/control status	-			
339373	somatic dem	somatic demo		Drag samples from the lef			ag to reo	order samples. The	eir order here determines	their
407935	LP6005815-0	LP6005815-DNA_C10	LP6005815-DNA_C10	order within the analysis v						
267687	PGP171	PGP171	myopia dataset	Use samples from refere	nce genome	GRCh37/HG19	▼ for t	his analysis.	Load from prior analy	sis
				Search samples by keyw	ord			7 Cases (affected,	tumor, responder, etc.)	
267692	PGP81	PGP81	myopia dataset	Name	Subiect	Created	T	187523238		
366070	treatment_vie	treatment_view1		187522886	221	12/16/15 04:49 PM		187523102		
267674	PGP100	PGP100	mvopia dataset	187522887	222	12/16/15 04:49 PM	- H	187523100		
				187522884	219	12/16/15 04:49 PM		187523092		
				187522885	220	12/16/15 04:49 PM		187523125		
				187523127	125	12/16/15 04:49 PM		187523091		
				187523270	126	12/16/15 04:49 PM		187523089		
				187523256	123	12/16/15 04:49 PM				
				187523078	155	12/16/15 04:49 PM				
				187523081	156	12/16/15 04:49 PM				
				187523119	169	12/16/15 04:49 PM				
				187523121	170	12/16/15 04:49 PM				
				187523057	168	12/16/15 04:49 PM				
				187523053	167	12/16/15 04:49 PM	(PGP-60 Library		
				187523047	165	12/16/15 04:49 PM		FGF-00 Library		
				187523048	166	12/16/15 04:49 PM	V	Use individual s	samples	
				Back					1	Vext

Export directly to IPA with inferred gain/loss-of-function values

A-Z SORT SEARCH REFRESH	<u>ड</u>								
My Projects	innotated Dataset: Preview Dataset 20				· · ·		(66)		r 9,
EEC From JN	Mapped IDs (66)	Unmapped IDs (0)	All IDs (66)				(00)		
🕀 🚞 Rupert_IPA_Test	Variant AC	Variant Gai		Notes	📥 🖳	Entrez Gene 🕱	Location 💌	Type(s)	Drug(s)
🕀 🛅 Variant Analysis		0.000	ABHD16A			abhydrolase dom		other	
🕀 🛅 Training Project	0.000	0.000	ADAT3		ADAT3	adenosine deami		enzyme	
	0.000	0.000	ANKRD29		ANKRD29	ankyrin repeat do	Other	other	
🕀 🚞 Ingenuity KEGG gene lists	0.000	+ -1.000	ANKRD36C		ANKRD36C	ankyrin repeat do	Other	other	
🕀 🛅 Human Genes Chromosomal Locatic	0.000	↓ -1.000	APC2		APC2	adenomatosis po	Cytoplasm	enzyme	
🕀 📄 Example Analyses	0.000	0 + -1.000			BCORL1	BCL6 corepressor.	Nucleus	transcription reg	
	0.000	0.000	C12orf40		C12orf40	chromosome 12	Other	other	
🗄 📄 Tissue Expression	0.000	0.000	CIC		CIC	capicua transcrip	Other	other	
🔧 Shared Projects			CLCN3		CLCN3	chloride channel,.	Plasma Membrane		
		0.000	CLDN25		CLDN25		Plasma Membrane		
🕀 🔩 Projects Shared with Others			CLTC			clathrin, heavy c			
🗄 📲 Projects Shared with Me		↓ -1.000	COG3			component of oli		transporter	
Libraries		0.000	COL14A1			collagen, type XI			collagenase clost
		↓ -1.000	CPSF3			cleavage and pol		enzyme	
	0.000	↓ -1.000	DHX40				Other	enzyme	
			EHMT1		EHMT1		Nucleus	transcription reg	
			FAM134B			family with sequ		other	
		0.000	HELQ		HELQ	helicase, POLQ-li	Nucleus	enzyme	
	0 / 66	n non							
	Molecular Network "O" - Override mole	cules. Gene/Proteir Chemical ID marke	/Chemical identifie	d with an asterisk ind ers marked as "Overr ne/protein/chemica	ide" are displayed w	ith italic text.	·		



www.allelefrequencycommunity.org

- Leverage the world's largest pool of anonymized allele frequency data
- Reduces false positives in analyses by removing variants that are commonly seen in the general population
- Contains Whole Exome AND Whole Genome data
- Better representation of Insertions and Deletions

Larger than ANY other public resource

- □ AFC launched with 70,000 samples with >8,000 as whole genomes
- □ 12x larger than Exome Variant Server data
- The initial launch version of the database already provides a 43% average false positive rate reduction in a benchmarking set of whole-genome Diagnostic Odyssey cases
- AFC will grow as more people opt-in
 - Launched on 25th February 2015 with 70,000 Samples including 8,000 Whole Genomes
 - Currently at over 100,000 samples, including over 14,000 Whole Genome samples

Sample to Insight



Ingenuity Variant Analysis

- Easy to use, allows scientific iteration
 - □ Filter variants, real-time, based on both standard and proprietary criteria
- Provides variant filtering using public and proprietary databases
 Allele Frequency Community
- Powerful tools for genetic and statistical tests
- Relate variants to literature and biology
 - Narrow-down, discover, and prioritize variants based on literature findings, pathway and biological associations
- Integrate variants with GWAS, gene expression, or other gene or positional data using BED files