

## Supplementary information

**Supp. Table S1. A Complete List of Softwares Used for Computational Analysis of Assorted Point Mutations of K5/K14 from Published Resources.**

Service name	URL	Reference
<b>Stability changes prediction</b>		
CUPSAT	<a href="http://cupsat.tu-bs.de/">http://cupsat.tu-bs.de/</a>	(Parthiban V, Gromiha MM and Schomburg D, 2006)
PopMusic	<a href="http://babylone.ulb.ac.be/popmusic">http://babylone.ulb.ac.be/popmusic</a>	(Dehouck Y, Grosfils A, Folch B, et al., 2009)
<b>Pathogenic or not</b>		
PolyPhen-2	<a href="http://genetics.bwh.harvard.edu/pph2/">http://genetics.bwh.harvard.edu/pph2/</a>	(Adzhubei I, Jordan DM, Sunyaev SR, 2013)
SIFT	<a href="http://sift.jcvi.org/">http://sift.jcvi.org/</a>	(Kumar P, Henikoff S, Ng PC, 2009)
<b>Multiple sequence alignment</b>		
ClustalW	<a href="http://www.ebi.ac.uk/Tools/msa/clustalw2/">http://www.ebi.ac.uk/Tools/msa/clustalw2/</a>	(Kuo-Bin Li, 2003)
<b>Interatomic interaction</b>		
Ligplot	<a href="http://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/">http://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/</a>	(Wallace A C, Laskowski R A, Thornton J M., 1996)
CMA/CSU	<a href="http://ligin.weizmann.ac.il/cma/">http://ligin.weizmann.ac.il/cma/</a>	(Sobolev V., Sorokine A., Prilusky J., et al., 1999)
ESBRI	<a href="http://bioinformatica.isa.cnr.it/ESBRI/">http://bioinformatica.isa.cnr.it/ESBRI/</a>	(Sarakatsannis J.N., Duan Y, 2005)
<b>Steric clash</b>		
Chimera	<a href="https://www.cgl.ucsf.edu/chimera/">https://www.cgl.ucsf.edu/chimera/</a>	(Eric F. Pettersen, Thomas D. Goddard, Conrad C. Huang, et al., 2004)

**Supp. Table S2. Characterized groups of all point mutations on 2B domain of K5/K14.**

Group	Mutation
Same position Different A.A. Different phenotype	K5-A428T/V
	K5-I467L/T/M
	K14-R388C/G/H/P
	K14-I412E/N K14-A413T/P
Same position Same A.A. Different phenotype	K5-E475K/G
	K14-I377N/T
	K14-R388C/H/P
Same position Different A.A. Same phenotype	K14-I377N
	K14-E381K
	K14-E411K
	K14-Y415H
Single mutation	K5-K404E
	K5-A438D
	K5-K443N
	K5-L463P
	K5-E466D
	K5-T469P
	K5-R471C
	K5-G476D
	K14-L384P
	K14-L401P
	K14-L408M
	K14-R416P
	K14-R417P
	K14-L418V
	K14-L419Q

**Supp. Table S3. Probable rotamers and corresponding interatomic clashes predicted with UCSF Chimera.**

K5-K404E	R1 (0.196): No Clash.
	R2 (0.162): No Clash.
	R3 (0.082): No Clash.
	R4 (0.082): Three contacts with Q348.a. Clashes disappeared after three steps with structure minimization of UCSF Chimera.
	R5 (0.072): No Clash.
K5-A428T	R1 (0.876): Three contacts with I373.a and I377.a. Clashes disappeared after three steps.
	R2 (0.116): No clash.
	R3 (0.008): One contact with L425.b, Clashes disappeared when adding H-atoms.
K5-A428V	R1 (0.918): Two contacts with I373.a and I377.a. Clashes disappeared after six steps.
	R2 (0.052): Three contacts with L435.b, I373.a and I377.a. Clashes disappeared after three steps
	R3 (0.030): One contact with L435.b. Clashes disappeared after three steps
K5-A438D	R1 (0.570): No clash
	R2 (0.150): Two contacts with L384.a and R388.a. Clashes disappeared after 15 steps
	R3 (0.138): No clash
	R4 (0.053): One contact with R388.a. Clashes disappeared after three steps
	R5 (0.034): One contact with E434.b. Clashes disappeared after three steps
K5-K443N	R1 (0.450): No clash.
	R2 (0.143): No clash.
	R3 (0.094): No clash.
	R4 (0.061): No clash.
	R5 (0.057): No clash.
K5-L463P	R1 (0.832): Five contacts with T460.b and L460.b. Clashes disappeared after three steps
	R2 (0.168): Three contacts with T460.b and L460.b. Clashes disappeared after three steps
K5-E466D*	R1 (0.478): One contact with Y470.b. Clashes disappeared after three steps
	R2 (0.207): Five contacts with Y470.b. Clashes disappeared after 39 steps
	R3 (0.145): One contact with Y470.b. Clashes disappeared after three steps
	R4 (0.071): Six contacts with Y470.b. Clashes disappeared after nine steps
	R5 (0.035): Six contacts with Y470.b. Clashes disappeared after 36 steps
K5-I467L	R1 (0.47): Two contacts with Y415.a, and the structure cannot be accommodated after 50 steps
	R2 (0.46): No clash.
	R3 (0.04): Three contacts with R471.b, and the structure cannot be accommodated after 50 steps
	R4 (0.015): One contact with I412.a, and the structure cannot be accommodated after 50 steps
	R5 (0.01): Six contacts with R471.b and Y415.a, and the structure cannot be accommodated after 50 steps
K5-I467M	R1 (0.19): Two contacts with I412.a. Clashes disappeared after three steps
	R2 (0.14): One contact with Y415.a, and the structure cannot be accommodated after 50 steps
	R3 (0.12): Two contacts with R471.b. Clashes disappeared after three steps
	R4 (0.11): Two contacts with L408.a. Clashes disappeared after three steps
	R5 (0.10): Two contacts with E411.a. Clashes disappeared after three steps
K5-I467T	R1 (0.966): No clash.
	R2 (0.031): No clash.
	R3 (0.003): No clash.
K5-T469P	R1 (0.531): Three contacts with V465.b. Clashes disappeared after 36 steps.
	R2 (0.169): Two contacts with V465.b. Clashes disappeared after six steps
K5-R471C	R1 (0.546): No clash.
	R2 (0.424): No clash.
	R3 (0.030): No clash.
K5-E475K	R1 (0.415): No clash.
	R2 (0.138): No clash.
	R3 (0.100): No clash.
	R4 (0.059): No clash.
	R5 (0.056): No clash.
K5-E475G	No rotamer and no clash.
K5-G476D	R1 (0.309): No clash.

	R2 (0.195): No clash.
	R3 (0.176): No clash.
	R4 (0.110): No clash.
	R5 (0.087): No clash.
K14-I377N	R1 (0.450): No clash.
	R2 (0.143): One contact with L435.b. Clashes disappeared after three steps
	R3 (0.094): No clash.
	R4 (0.061): Two contacts with L431.b and L435.b, and the structure cannot be accommodated after 50 steps
	R5 (0.057): One contact with L435.b, and the structure cannot be accommodated after 50 steps
K14-I377T	R1 (0.909): No clash.
	R2 (0.078): No clash.
	R3 (0.013): One contact with Q374.a. Clashes disappeared after three steps
K14-E381K	R1 (0.272): No clash.
	R2 (0.129): Three contacts with I377.a and K431.b. Clashes disappeared after 21 steps
	R3 (0.084): No clash.
	R4 (0.066): No clash.
	R5 (0.057): No clash.
K14-L384P	R1 (0.724): Three contacts with V380.a, and the structure cannot be accommodated after 50 steps
	R2 (0.276): Eight contacts with V380.a and E381.a, and the structure cannot be accommodated after 50 steps
K14-R388C	R1 (0.697): No clash.
	R2 (0.233): No clash.
	R3 (0.070): One contact with A385.a. Clashes disappeared after three steps
K14-R388G	No rotamer and no clash.
K14-R388H	R1 (0.307): No clash.
	R2 (0.177): One contact with L384.a. Clashes disappeared after three steps
	R3 (0.166): No clash.
	R4 (0.160): No clash.
	R5 (0.087): Two contacts with L384.a. Clashes disappeared after 15 steps
K14-R388P	R1 (0.724): Five contacts with L384.a and A385.a, and the structure cannot be accommodated after 50 steps
	R2 (0.276): Eight contacts with L384.a and A385.a. Clashes disappeared after 18 steps
K14-L401P	R1 (0.915): Four contacts with E397.a and Y453.b, and the structure cannot be accommodated after 50 steps
	R2 (0.085): Four contacts with E397.a and Y398.a, and the structure cannot be accommodated after 50 steps
K14-E411K	R1 (0.285): Five contacts with Y415.a and I467.b. Clashes disappeared after 18 steps
	R2 (0.122): No clash.
	R3 (0.083): Ten contacts with Y415.a and I467.b, and the structure cannot be accommodated after 50 steps
	R4 (0.067): Nine contacts with Y415.a and I467.b, and the structure cannot be accommodated after 50 steps
	R5 (0.049): Seven contacts with Y415.a and I467.b. Clashes disappeared after three steps
K14-I412F	R1 (0.776): Seventeen contacts with Y470.b and Y415.a, and the structure cannot be accommodated after 50 steps
	R2 (0.135): Six contacts with L463.b, E466.b and I467.b. Clashes disappeared after 48 steps
	R3 (0.039): Seventeen contacts with E409.a and Q410.a, and the structure cannot be accommodated after 50 steps
	R4 (0.024): Eleven contacts with E409.a, and the structure cannot be accommodated after 50 steps
	R5 (0.016): Seventeen contacts with Y470.b and R416.a, and the structure cannot be accommodated after 50 steps
K14-I412N	R1 (0.369): No clash.
	R2 (0.133): No clash.
	R3 (0.125): No clash.
	R4 (0.063): No clash.
	R5 (0.059): No clash.
K14-A413T	R1 (0.515): One contact with E409.a. Clashes disappeared after six steps
	R2 (0.456): No clash.
	R3 (0.029): One contact with Q410.a. Clashes disappeared after three steps
K14-A413P	R1 (0.629): Ten contacts with E409.a, Q410.a and E411.a. Clashes disappeared after three steps
	R2 (0.371): Seven contacts with E409.a and Q410.a. Clashes disappeared after 36 steps
K14-Y415H	R1 (0.495): Eleven contacts with Y470.b and L474.b. Clashes disappeared after 42 steps
	R2 (0.185): Twelve contacts with Y470.b and L474.b, and the structure cannot be accommodated after 50 steps
	R3 (0.185): Twelve contacts with Y470.b and L474.b, and the structure cannot be accommodated after 50 steps
	R4 (0.074): No clash.
	R5 (0.048): No clash.
K14-Y415C	R1 (0.545): No clash.
	R2 (0.424): One contact with Y 470.b. Clashes disappeared after three steps

	R3 (0.030): One contact with I412.a. Clashes disappeared after three steps
K14-R416P	R1 (0.707): Three contacts with I412.a, and the structure cannot be accommodated after 50 steps
	R2 (0.293): Three contacts with I412.a, and the structure cannot be accommodated after 50 steps
K14-R417P	R1 (0.850): Twelve contacts with A413.a, T414.a and Y415.a. Clashes disappeared after six steps
	R2 (0.150): Ten contacts with A413.a, T414.a and Y415.a. Clashes disappeared after 36 steps
K14-L418V	R1 (0.524): No clash.
	R2 (0.298): No clash.
	R3 (0.177): No clash.
K14-L419Q	R1 (0.229): No clash.
	R2 (0.124): No clash.
	R3 (0.123): No clash.
	R4 (0.087): Three contacts with L474.b. Clashes disappeared after six steps
	R5 (0.083): No clash.

#1: We only select top five rotamers of each point mutation.

#2: K5-E466D\*: there is a default clash: E466.b O---2.542---Y470.b CD<sub>2</sub>.

#3: R1 (0.229) denotes the first rotamer and corresponding probability is 22.9%.