

Electronic Supplementary Information, ESI

Identification of the Functional States of Human Vitamin K Epoxide Reductase from Molecular Dynamics Simulations

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- A. Figures S1- S11
- B. Table S1
- C. Modelling Methods
- D. PDB files contain the

atomic coordinates of the

models

Functional States of VKOR/N. Chatron at al.

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Electronic Supplementary Information (ESI) available: [11 Figures, 1 Table and Methods details]. See DOI: 10.1039/x0xx00000x



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Fig. S1 Validation of the methods used for prediction of secondary structure. The bVKOR topology and its membrane content were predicted by 8 different methods for each kind of forecast. Two types of consensus– for the secondary structure prediction and for the membrane content prediction–were considered. The secondary structure interpretation (DSSP) of the crystallographic structure 1NV5.

	10 MASYLKLKAQ	20 EETWLQRHSR	30 LILAILAGLG	40 SLLTAYLTYT	50 KLTEQPAAFC	60 TGDGGCDLVL	70 SSRWAEFLGI	80 PTAAVGLLGF
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JFred	170 FSYILVAFLT	180 LVTTIGVYAN	190 QVPPPSPLAV SSEHEH	200 GLAAHLRQIG HHENHHHE	210 GTMYGAYWCP	220 HCQDQKELFG EHERHEREN	230 AAFDQVPYVE HHEHSS	240 CSPNGPGTPQ SH
JPred GOR4 PsiPred	170 FSYILVAFLT SSSSS- HEHEHEHEH HEHEEHEHEH	180 LVTTIGVYAN SSSSS3 H	190 QVPPPSPLAV SSEHHH 	200 GLAAHLRQIG ИНИНИЦИИ ИНИНИНИИ ИНИНИНИИ	210 GTMYGAYWCP -SSS SSSSSSS	220 НСQDQXELF9 ЕНЕННЕНЕНИ ЕНЕННЕНЕНИ	230 AAFDQVPYVE 	240 CSPNGPGTPQ SH SH
JFred GOR4 PsiFred SS FSIFRSD SS JNST	170 FSYILVAFLT SSSSS- HEHEHEHH- HINHEHEHEH HINHEHEHEH	180 LVTTIGVYAN SSSSS H-HHEHEHEH HHHEHEHEH	190 QVPPPSPLAV SS	200 GLAAHLRQIG HHENHHHHI HHENHHHHI HHENHHHH HHENHHHH	210 GTMYGAYWCP -555	220 НСОДОКЕЛЕЭ ЕНИИНЕННИ НИИНЕННИ ПИПИНЕННИ НИИНЕННИ	230 AAFDQVPYVE HHEH	240 CSPNGPGTPQ SH S
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Fig. S2 The homology modeling of hVKORC1. (A) Alignment of the sequence's segment (13-181 residues) of bVKOR with the sequence of hVKORC1. The identical residues are distinguished by grey background; the similar residues are shown in blue. The secondary structure interpretation of the template sequence (top) and the predicted secondary structure composition (consensus) of the target sequence (below) are shown. (B) Structure 4NV5 of the bVKOR is presented as cartoon. The structural fragment showing the best sequence similarity with hVKORC1 is denoted in orange. (C) The hVKORC1 topology and its membrane content were predicted by 8 different methods for each kind of forecast. Two types of consensus – for the secondary structure prediction and for the membrane content prediction – were schematized (in deep teal).

Α											
bvkor hvkorc1	TM-LQRISRLITAXILTYTKLTEQPARGT MGSTMGSPGWVRIALCTGLVISLVALIVKARARDRDVRALC- 1030 40		PTAVGI SQDSILNQSNSIFGO 80	LGFLGVLALAVLE IFYTLQLLLGCL- 90	DGLPLVKRWRWPA	LFGLVSAMTAF	VENYMLYLMVAVLI SVYLAWILFFVL 120 1	RQFCMYCTTAILLY YDFCIVCITTYAII 30 140	VAGLGLVTVLGHR	VLD VLSFRKVQEPQGKA 150 160	AKRH
	TM1	нн		TM2			ТМЗ	Т	M4		
В		С	10 MGSTWGSPGW	20 VRLALCLTGL	30 VLSLYALHVK	40 AARARDEDYR	50 ALCDVGTAIS	60 CSRVFS SRWG	70 RGFGLVEHVL	80 GODSILNOSN	
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Fig. S3 Hydrophobic interactions stabilising the hVKORC1 structure of. Protein is presented in two orthogonal views as cartoon with the hydrophobic residues showed as space-filling spheres.



Fig. S4 Structural features of hVKORC1. (A) The secondary structure assignment for protein was done for each 1- μ s trajectory, 1" (top) and 3" (bottom). The α -helix, 3¹⁰ helix, β -bridge, turn and loop are shown in red, orange, light-green, blue and cyan, respectively, and referred to the predicted helices. (B) Drift of helices was monitored over the extended simulations 1" (left) and 3" (right). Two centroids, assigned on the last four residues at the top and at the bottom of each helix, were defined. A sole centroid for HH was assign on seven residues. . Coordinates of each centroid were computed for each MD simulation time step and presented as the lines connecting the two TM centroids, in 3D space (top) and as the points projected on the *x*-*y* plane (bottom) coloured from blue (t=0) to cyan (t=1 μ s) for the top of TM helices; from black (t=0) to green (t=1 μ s) for the bottom; and from red (t=0) to yellow (t=1 μ s) for HH.



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Fig. S5 Molecular dynamics simulation of hVKORC1. The RMSFs profiles of the short (100 ns 1, 2 and 3) and extended (1- μ s) simulations 1" and 3". The RMSFs were computed on the C α atoms.



Fig. S6 Global motions and their correlations. The inter-residue cross-correlations maps resulting from PCA of the short (100 ns) (left) and extended to 500 ns (middle) and to 1 μ s (right) trajectories, **1**" (the upper half-matrix) and **3**" (the lower half-matrix). Correlated (positive) and anti-correlated (negative) motions between atom pairs are presented as a gradient between red and color colors.



Fig. S7 Spectral analysis of trajectory 3" **after PCA**. (A) Similarity matrix W; (B) The largest eigenvalues; (C) First slow variable; (D) Second slow variable. By searching the changes of sign of this slow variable, it appears that the main basin is approximately located between the frame12500 (t=250 ns) and the frame 30000 (t=600 ns), and the second basin between the frame 37500 (t=750 ns) and the



Fig. S8 Spectral analysis of trajectory 3" without PCA reduction. (A) Similarity matrix W; (B) The largest eigenvalues; (C) First slow variable; (D) Second slow variable.



Fig. S9. Structural features of models M¹-M¹V. (A) The secondary structure evolution over MD simulations (all trajectories were merged). The α -helix, 3¹⁰ helix, β -bridge, turn and loop are shown in red, orange, light-green, blue and cyan, respectively, and referred to the predicted helices (top). For each model, the cysteine residues forming S•••S bridge is noted at top.





Fig. S10. The clusters of conformations defined with cutoff of 2.0 Å and their population (in %) calculated for MD simulation (2x100 ns) of models M^{I} - M^{IV} . For each model, the cysteine residues forming S•••S bridge is noted at top.





C43-C51 C132-C135

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Fig. S11. Molecular dynamics simulations of the hVKORC1 complexes. (A) The RMSDs from the initial coordinates (t=0 ns) are computed on the C α atoms of 100-ns MD trajectories of vitK^{EP}•T^{III} (green) and vitK^{2-OH}•T^{IV} (red). (B) The RMSFs are computed on the C α atoms over of 100-ns MD trajectories of vitK^{EP}•T^{III} (green) and vitK^{2-OH}•T^{IV} (red). (C) The RMSDs from the initial coordinates (t=0 ns) are computed on the C α atoms of 100-ns MD trajectories of A•T^{III} (violet), D•T^{III} (orange) and P•T^{III} (purple) ad W•T^{III} (cyan). (D) The RMSFs are computed on the C α atoms over of 100-ns MD trajectories of A•T^{III} (violet), D•T^{III} (orange) and P•T^{III} (purple) ad W•T^{III} (cyan).



C. Table S1

Table S1. Crystallographic structures of VKOR reported in ProteinData Base (PDB) [1]. The PDB identification code (ID), resolution(Res, in Å), the sequence length, missing residues, mutated residues,cysteine residues, distances (d, in Å) between the sulfur atoms fromcysteine residues and reference are denoted for each structure.

PDB ID	Res, (Å)	Sequence length	Missing residues	Cysteine**	S…S, d (Å)	Ref
3KP9	3.6	16 - 279	53-55, 91-92	C50(43), C56S(51) C130(132), C133(135)	C50S56, 13 S56C130, 8 C130C133, 2	[2]
4NV2	3.6	17 - 282	92-93	C50A(43), C56S(51), C130(132), C133(135)	A50…C56, 4 C56…C130, 2 C130…C133, 4	[3]
4NV5 A*	2.8	17 - 282	49-53, 92,155	C56(51), C130(132), C133(135)	C56…C130, 2 C130…C133, 4	[3]
4NV5 B*	2.8	13 - 279	49-53	C56(51), C130(132), C133(135)	C56…C130, 2 C130…C133, 4	[3]
4NV6	4.2	17 - 282	92, 155	C50(43), C56(51) C130(132), C133(135)	C50C56, 14 C56C130, 2 C130C133, 4	[3]

*Two chains, A and B.

**The cysteine residue or its mutant, as numbered in a structure sequence and its corresponding number in hVKORC1 sequence denoted in brackets.

C. Modelling Methods

1. Secondary structure prediction

PREDATOR [4] algorithm is based on potentially hydrogenbonded residues recognition in the target sequence using a structural database information. First, the propensity of residues to form α -helix or β -sheet type hydrogen bonds is calculated for each single residue. Then, for each residue, the influence of the nearest neighbors is considered. Finally, the secondary structure consensus is established for each residue, by combination of the two predictions.

GOR IV [5] uses information theory and Bayesian statistics to calculate the propensity of each residue from the target sequence to

form specific secondary structure, considering the nearest neighbors of the local segment.

PSIPRED [6] is based on position-specific scoring matrices (PPSM) combined to neural network application. The target sequence is submitted to the PSI-BLAST algorithm and, after three iterations, the PPSM is picked. This matrix is then split in fifteen residues length windows, each one used as input for the neural network. A second neural network filters successive outputs from the first one. Ten percent of the data is kept aside as an evaluation set. The neural network is trained on the remaining data for weights optimization,

ARTICLE

according to an on-line back-propagation procedure. Training is stopped when the accuracy of the network on the evaluation set starts to decrease.

PROF [7] is based on neural network, but requires five steps. This algorithm starts with GOR method, complemented with evolutionary information. The predicted by GOR results, combined with neural networks, are trained either in an unbalanced or in a balanced way using different profiles, producing the classifiers. The results are analyzed by linear discrimination or neural networks, yielding new classifiers which are then used again for a training. Finally, the two resulting classifiers are averaged to give a unique prediction for each residue.

JPRED [8], a consensus secondary structure predictor, uses evolutionary information and is based on six methods – NNSSP (nearest neighbors prediction), PHD (a jury decision neural networks), DSC (linear discrimination), MULPRED (a consensus single sequence method combination), ZPRED (conservation number weighted prediction) and PREDATOR (hydrogen bonding propensities).

2. Topology prediction

HMMTOP [9] predicts the localization of helical transmembrane segments and the topology of transmembrane proteins. It bases on the concept, that the transmembrane proteins topology is determined by the maximum divergence of amino acid composition of sequence segments. The method localizes certain sequence segments in areas used as structural parts (inside, outside, inside helix tail, outside helix tail and membrane helix). The method accuracy is enhanced by hidden Markov model, which controls the different segments length.

OCTOPUS [10] uses a combination of hidden Markov models and artificial neural networks. It first performs a homology search using BLAST to create a sequence profile used as the input to a set of neural networks which predict the location preference for each residue – transmembrane, interface, globular, loop, inside or outside. These predictions are used as input to a two-track hidden Markov model, which uses them to calculate the most likely topology. Results of these two sets are finally combined to obtain each residue preference.

SPOCTOPUS [11] uses the same algorithm as OCTOPUS, enforced with a predicting the signal peptide in the target sequence. Location of residues from this signal peptide is determined by a hidden Markov model prior the topology prediction by OCTOPUS, providing more accurate topology prediction.

PHOBIUS and POLYPHOBIUS [12] use a hidden Markov model, decoding algorithm that combines probabilities for sequence features of homologs by considering the average of the posterior label probability of each position in a global sequence alignment.

PHILIUS [13] (www.yeastrc.org/philius) is based on a hidden Markov model similarly to PHOBIUS and POLYPHOBIUS, expanded to using the more powerful class of dynamic Bayesian networks.

SCAMPI [14], a simple generic topology model, uses a contribution of position-specific amino acids to the free energy of membrane insertion that performs on a par with the current best statistics-based topology predictors. It is similar to a hidden Markov model in the sense that states and state transitions are used to define an underlying grammar.

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S1. The atomic coordinates of the $\ensuremath{\mathsf{vitK}^{\mathsf{EP}}}\xspace{-hVKORC1}$ complex at t=0

S1-1 and S1-2. The atomic coordinates of the vitK^{EP}-hVKORC1 complex at t=100 ns of each replica (1 and 2)

S2. The atomic coordinates of the W-hVKORC1 complex at t=0

S2-1 and S2-2. The atomic coordinates of the W-hVKORC1 complex at t=100 ns of each replica (1 and 2)