

Web page supplement to paper:

Sequence based prediction of linear autoepitopes involved in pathogenesis of IPAH and the corresponding organism sources of molecular mimicry

WP1. Some important features concerning our evaluation of DQPA occurrences in sequence database (i.e. SPECIES_VALENCE approach). SP_VAL is based on four important features of our evaluation. First of all, the consistent threshold of the selected DQPA represents an important parameter of specificity together with overall BLAST evaluation of DQPA similarities. Secondly, SP_VAL as propensity-related approach makes it possible to process less favorable DQPA identities evaluated as important in some cases of higher frequency. Thirdly, implemented empirical statistics of SDF and EDO values can be used even under otherwise hardly processable conditions. Fourthly, alternative models are included to better analyze different aspects of evaluated reality.

WP2 DQPA as potential autoepitope-related structures. Sequences of both F1SA and autoantigens represent in fact knowledge-based reservoirs of autoepitope structures. Consequently, dense short DQPA present simultaneously in both types of sequences form a concentrated set of potential autoepitopes (cf. 2.1). Since the set of IPAH related autoantigens is possibly still incomplete, we classify here preselected organisms (with DQPA related proteins) according to the presence of DQPA in IPAH related autoantigens or in a more extended set of autoantigens restricted by ScanProsite program and the proposed HMG relationship (Morse et al., 1996; cf. Table 3).

WP3 Nonapeptides form the longest DQPA-related sequences in our model. Nonapeptides interact with antibodies recognizing linear epitopes with high affinity (Königs et al., 2000; Afonin et al., 2001). Stereochemical models of

antibody interaction with nonapeptides then suggest complete overlap of antibody binding site by nonapeptides (Afonin et al., 2001).

WP4 Expansion to eight model situations. Different model situations in fact reflect considered variability of possible relationships, alternative explanations or existing events including current behavior of bacterial infection (cf. section 2.1 and Table 3). In addition, we test here the stability of achieved differences with respect to given variability, when using mean values and criteria mentioned in 3.3.

WP5 Some aspects of information bias. The set of organisms involved in respiratory diseases S1.2 is favorably optimized owing to i) more extensive sequencing in the area of medical microbiology and ii) frequencies of DQPA. Consequently, the application of the two different approaches of empirical statistics based on S1.2-related RSO set of hashes as reference set can usefully restrict limits with respect to contemporary status of sequencing, possible random relationships and some false positivities. This is why we speak here about organisms outside our selection instead of definitive decision.

WP6 References to reference set S1.2. All organisms of the reference S1.2 set (cf. also section 2.3) displayed here represent pathogens or commensals involved in acute bronchitis (MacKay et al., 1996), lung abscess (Mori et al., 1993; Hirshberg et al., 1999), acute pharyngitis (Bills et al., 1996), tuberculosis and pneumonias. The last group of diseases then includes **viral** pneumonias (Oda et al., 1994; Chien and Johnson, 2000), HIV-associated **opportunistic** pneumonias (Huang and Crothers, 2009; King et al., 2009), **bacterial** pneumonias (Marrie et al., 1998; Niederman et al., 2005; Yildiz and Dagonay, 2006), **fungal** pneumonias (Conces, 1999; Saubolle, 2000) or **differently**

(otherwise) **classified** pneumonias (Azevedo Sias et al., 2009; Niederman et al., 2005).

WP7 Formulas necessary for evaluation of DQPA set. The limit of valid sequence probability ($P < \text{MAX}(P)$, where MAX is the maximum possible value under the condition $p < w$; w is 0.05 in our case) for local occurrences of **nonrandom dense aa sequence** can be derived using different procedures. In accordance with binomial statistics, we determined $\text{MAX}(P) = 2.5063 \times 10^{-3}$ (cf. Lepš, 1996; Kubrycht et al., 2006; Kubrycht and Sigler, 2008). An alternative slightly higher probability limit ($\text{MAX}(P) = 2,7625 \times 10^{-3}$) follows also from a case when both *a priori* and *a posteriori* Bayesian probabilities are limited by the same significance level $p < 0.05$ (i.e. $p < w$; $w(P|w) = 0.05$; $w = 0.05$). The corresponding formula is in fact equation in the case of unknown limiting $P = \text{MAX}(P)$ (cf. Zimmer, 2004):

$$w(P|w) = P \times (1 - w) / (P \times (1 - w) + (1 - P) \times w), \quad (\text{WF1})$$

Since local probability values of sequence identities (LPSI) are usually higher than the corresponding local random chain probabilities mentioned above, we can assume that the conventional limit used for pattern-related PSI-BLAST restriction $p < 0.005$ (Altschul et al., 1997) is sufficient to limit LPSI related Expects of DQPA identities. This Expects represent in fact minimum possible Expect of each query sequence ($E_{\min,i}$):

$$E_{\min,i} = K \times H \times L_i^2 \times \exp(-\lambda \times S_i). \quad (\text{WF2})$$

where K , H , λ are usual BLAST constants for ungapped BLASTP search ($K = 0.2891920$; $H = 1.935981$; $\lambda = 0.294$); L_i is length of i -th DQPA.

Significance levels ($p < w$) of $E_{\min,i}$ easily follow from general BLAST-related formula (Altschul, 1990), which holds also for $E = E_{\min,i}$:

$$w = 1 - \exp(-E), \quad (\text{WF3})$$

If we assume that addition of sufficiently restricted DQPA-related chains to the sequence set cannot negatively influence Expect evaluation, then overall

Expect evaluation related to multiple DQPA occurrence in the database depends mainly on individual Expects of lowest values. Hence such Expects indicate the similarities of the highest validity. The contribution of other DQPA then increases with the number of their identities. Under such conditions, the corresponding relationship between individual Expect values (E_i) and overall expect (E_h) is related to the EDO evaluation mentioned above and can be modeled by harmonic evaluation:

$$E_h = N_w \times E_1 \times E_2 \times E_3 \times E_n / \{(E_2 \times E_3 \times \dots \times E_n) + (E_1 \times E_3 \times \dots \times E_n) + \dots + (E_1 \times E_2 \times E_3 \times \dots \times E_{n-1})\} = N_w / (1/E_1 + 1/E_2 + 1/E_3 + \dots + 1/E_n), \quad (\text{WF4})$$

where N_w denotes the number of window shifts restricting here the length of linear epitopes and can be easily enumerated, i.e. $N_w = (\delta - (W - 1))$. In accordance with the usual linear epitope extent we employed the window of length $W = 9$ (cf. section WP3) to cover F1SA sequence of length $\delta = 123$, i.e. $N_w = 115$.

The modified formula for individual Expect enumeration differs from the original BLAST formula only in the existence of specific DQPA-related database length M_i (cf. also formula 2):

$$E_i = K \times H \times L_i \times M_i \times \exp(-\lambda \times S_i) \quad (\text{WF5})$$

More precisely, M_i denotes effective database length of huAG corrected with respect to i -th DQPA length:

$$M_i = D - Q \times (L_i - 1) \quad (\text{WF6})$$

where Q is the number of autoantigen molecules ($Q = 140$); D is full database length, i.e. $D = \sum_{j=1}^J C_j = 95\,469$, where C_j are chain lengths of separate sequences.

Full database length of huAG, i.e. D , is the sum of all chain lengths of the sequence set comprising autoantigens linked to IPAHA, autoantigens forming a pre-restricted explicit autoantigen subset in ScanProsite, and HMG proteins of not fully restricted linkage to IPAHA and autoimmune diseases. HMG were restricted by BLASTP comparison with RPS-BLAST-derived consensus of

HMG superfamily-related conserved domain as a sequence query (conventionally limited by $p < 0.005$) and reevaluated for conserved domain HMG-related similarities.

Like other sequence similarities of length 5-15 aa length, 5-9 aa long DQPA identities can be evaluated by means of “BLASTP search for short near exact matches” (SNEM BLASTP) using PAM30 substitution matrix. SNEM BLASTP is restricted by limits two hundred times higher than usual BLASTP. Consequently, the modified significance level of the selected DQPA set ($p < w_{DS}$) can be approximated by the following formula:

$$w_{DS} = 1 - \exp\{-E_h/200\} \quad (\text{WF7})$$

Provided that enumerated DQPA similarities are sufficiently robust (see section WP8), we can use current significance limit $p < w_{DS} \leq 0.05$. In such case, we speak here about the valid SNEM BLAST similarity based on $p < w_{DS}$.

Related evaluations of DQPA occurrences in the compared microorganism sequence sets were not performed. Hence the majority of Expects values was higher than all usual significance limits due to frequent cases of database lengths higher than 10^6 . Moreover, additional problems moreover follow also from the incompleteness or redundancy of current databases. Such state thus in fact implicates usage of empirical statistics described in sections 2.7-2.9 as a possible starting point.

WP8. DQPA set is sufficiently robust to use $p < 0.05$. Since random binomial and Bayesian evaluations are highly related in the range of usual limiting values $w = 0.05$ (Kubrycht et al., 2006), it is possible to delimitate significance limits using combined evaluation. Based on binomial statistics, we can enumerate the validity of a set containing s structures (i.e. set of sample size s) of significance level restricted by $p < w[s]$ (Lepš, 1996):

$$w[s] = (r \times (1-r)/s)^{0.5}, \quad (\text{WF8})$$

where r is a random chain probability. Formula WF8 enables to derive simple recurrent enumeration:

$$w[s] = (1/s)^{0.5} \times w[1] \quad (\text{WF9})$$

Formula WF9 and $w[1]$ value are then necessary for the enumeration confirming the validity of $w[s]$ with respect to sample size and predetermined significance level w . The evaluation is in principle identical with the evaluation represented by formula WF1:

$$w(w[s]|w) = (1-w) \times w[s] / \{(1-w) \times w[s] + w \times (1 - w[s])\} \quad (\text{WF10})$$

As mentioned in section WP7, the value $w[1] = P = 0.005$ sufficiently restricts the pattern-related minimum Expect values corresponding to the limit of PSI-BLAST searches and also our DQPA comparisons. In accordance with this fact, we used a more strict combined Bayesian/binomial approach defined by formula WF10 (cf. section WP7) and unfavorable maximum $w[1]$ to delimitate a limit of s stricter than the true limit, but still sufficient for our decision. More precisely, we determined the minimum number of DQPA, whose Expect values are approximated by the enlarged values of unfavorable maximum $w[1] = 0.005$ and their occurrence is sufficient for a posteriori value $w(w[s]|w) \leq 0.05$ (defined by formula WF10 under the validity condition $w = w_{DS}$; cf. formula WPF7).

The enumerated critical sample size of the DQPA set was twelve in our case, which in fact corresponds to $s \leq 12$ in case of less strict Expect evaluation. This means that our set with 33 initial DQPA is sufficiently robust with respect to significance limit $p < 0.05$ for Expect value.

WP9 Why we use quasiconsistent level. The usage of **quasi-consistent significance level $p < 0.10$** is sometimes proposed in statistical tables as maximal limiting value instead of usual limit 0.05. Similarly, “negative big” values in fuzzy logic are limited by interval range 8.33% but not 5% (Jura, 2003), whereas the binomially derived significant occurrence level of

specifically recognized tetranucleotides achieves $p < 0.0896$ (Kubrycht and Sigler, 2008).

WP10. Additional relationships of DQPA to metalloproteinases and interleukins. Sequence of metalloproteinase ADAMTS16 contains other sequence VPRPP (Q11) of human SOX13 origin achieving the second REF related c_{im} . Q11 constitutes PAB-dependent poly(A)-specific ribonuclease subunit pan2 of both the selected *Aspergillus* species. DQPA YPPPP (Q5) of human Annexin A11 origin contains frequently immunogenic tyrosine together with multiple flexible prolines (i.e. potential flexible tyrosine; cf. section 4.1). This DQPA achieves forth highest value of c_{im} among all DQPA found in microorganisms. Q5 constitutes five different sequences of proteins synthesized by both selected pairs of *Mycobacterium* and *Aspergillus* genera and was also found in the sequence of human interleukin 34.

Metalloproteinase ADAMTS8 (found by using three different DQPA5) inhibits angiogenesis (Vázquez et al., 1999). Model ADAM15 deficient mouse (ADAM15 includes DQPA6 frequent PPPPXXPXP) shows reduced neovascularization compared with wild-type controls (Horiuchi et al., 2003). Interleukin 6, including *E.coli*-related DQPA5 PVPPG in its sequence, is a pro-inflammatory cytokine found in significantly higher amount in patients with severe IPAH (more than four times higher mean values) (Humbert et al., 1995).

WP11. Structural changes of proline - additional comments. Since the energy difference between trans- and cis-configurations of prolyl residues is very low in proteins, the corresponding **trans/cis-isomerization** can occur even spontaneously (Schmid, 1993; Chiang et al., 2009). In addition, this isomerization is also accelerated by prolyl-isomerases (Schmid, 1993; Wang and Etzkorn, 2006). The group of human proteins with prolyl isomerase activity includes cyclophilins, FKBP, and parvulin, although some larger proteins also

contain prolyl isomerase domains. Cyclophilin B present in human plasma and some molecules involved in infectivity of lung pathogenic organisms, e.g. *C.neoformans* selected here (Table 3), *Streptococcus pneumoniae* and *Legionella pneumophila* (Cianciotto et al. 1989; Ren et al., 2005; Hermans et al., 2006) represent the possible prolyl-isomerase sources in the extracellular space. This implicates the question of possible additive effects of bacterial prolyl-isomerases in the mechanism proposed here (e.g. in case of co-infecting pathogens). Chaperon activities of prolyl-isomerases were recently analyzed on structural level (Jakob et al., 2009). Hydroxylation of prolyls usually stabilizes fibrous poly-proline helix II. This means that the effects diminishing this **hydroxylation** can also participate in prolyl-related structural changes (Adzhubei and Sternberg, 1993; Adzhubei and Sternberg, 1994). Antibodies against proline rich epitopes have been screened in several diseases (De Keyser et al., 1992, Greene et al., 2010).

WP12. Some additional notes to the selected microbes and EDO values. *Pseudomonas aeruginosa* represents together with *Staphylococcus aureus* and *Acinetobacter baumannii* an organism of high frequency during hospital-acquired pneumonia (Beardsley et al., 2006) and is associated with high mortality rate during lung abscess (Hirshberg et al., 1999). Invasive aspergillosis is perhaps the most devastating of *Aspergillus*-related diseases, targeting severely immunocompromised patients (patients with AIDS and other hematological malignancies such as different leukemias, solid-organ and hematopoietic stem cell transplants, genetic immunodeficiencies such as chronic granulomatous, or on prolonged corticosteroid therapy; Dagenais et al. 2009). Noninvasive aspergillomas may form following repeated exposure to conidia and target preexisting lung cavities such as the healed lesions in tuberculosis patients (Dagenais et al. 2009). In multivariate analysis, the only significantly positive influencing factors on colonization by *Candida albicans* at the tongue

were tongue piercing ($p = 0.034$) and daily smoking of more than 10 cigarettes ($P = 0.024$; Zadik et al. 2010). The increased occurrence of *Candida* (predominantly *C. albicans*) in saliva and faeces of the psoriatic patients suggests at least adjuvant effects of this organism (Waldman et al., 2001). *Mycobacterium bovis* belongs to the group of highly related microorganisms (at boundary line of species and genus; perhaps in the range of sub-genus taxonomy) denoted as *Mycobacterium tuberculosis* complex and including also *M. tuberculosis*. This microorganism can also cause human tuberculosis and possibly also at least some of the autoimmune effects described in section 4.3 (O'Reilly and Daborn, 1995; Dubaniewicz et al., 2010; Homolka et al. 2010). Symbiotic bacteria *E. coli* causes community-acquired pneumonia in some cases (Marrie et al., 1998; cf. Table 3 and sections and 3.3 and 4.5).

In the case of cellular and combined immune deficiencies, not only bacterial infections but also the very serious opportunistic infections occur. Opportunistic lung infections are predominantly caused by cytomegalovirus (forming important combination with EBV in Table 3), two genera of fungi selected also in this paper, i.e. *Candida*, *Aspergillus*, and moreover by *Pneumocystis carinii* and fungi of genus *Mucor* (Ball, 1990). Similarly, organ transplantation can cause invasive mucosal infection such as aspegilloma, candidiasis and less frequently also similar infection with *Cryptococcus neoformans* (Pacholczyk et al., 2011).

It is a question, what is the cause of superior occurrence of *Staphylococcus aureus* (mentioned above) in blood cultures of PAH patients (49 of 192 patients) with central venous catheters (Oudiz et al., 2004). Though DQPA LXVNVT is responsible only for low positivity of IPA-related EDO value in case of *S. aureus*, this structure is present in sequence of pathogenically important molecule of staphylokinase. This molecule abolishes bactericidal properties of α -defensins and activates plasmin, a broad-spectrum proteolytic enzyme facilitating bacterial penetration into the surrounding tissues and alleviates the

course of *S. aureus* sepsis (Bokarewa et al., 2006; Kwieciński et al., 2010). In addition, the sequence of other pathogenically important protein clumping factor B (responsible for nasal colonization with *S. aureus* (O'Brien et al., 2002; Walsh et al., 2009) contains other DQPA PXPPVXPXP. In case of the detection of the corresponding autoantibody specificities, the preceding facts would raise the question of possible inclusion of expression-related parameter to formula 2.

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Table WT1. DQPA and some their properties (supplement to Table 2)

Sequence	DQPA name ¹	Occurrence ²	DQPA ⁿ ³	L _i ⁴	E _{min} ⁴	τ _i ⁴
Fundamental DQPA subset						
PQxPVPRP	Q1	SSA27	DQPA7-*	8	1.480E-5	3.30340E-6
PVPRPP	Q2	CHD4	DQPA6*	6	2.011E-5	5.98508E-6
PPRVLP	Q3	PTPR2	DQPA6*	6	2.698E-5	8.03069E-6
PxYPPPP	Q4	Annexin All	DQPA6	7	4.927E-5	1.25714E-5
YPPPP	Q5 = Q4a	Annexin All	DQPA5	5	6.072E-5	2.16921E-5
PPPPLxPxP	Q6	CHD3	DQPA7	9	8.144E-5	1.61632E-5
PPPLxPxPP	Q7	CHD3	DQPA7	9	8.144E-5	1.61632E-5
PxPPVLPxP	Q8	HMG TOX2	DQPA7*	9	1.093E-4	2.16875E-5
FPPGPxI	Q9	TG	DQPA6*	7	1.190E-4	3.03690E-5
PPPPLxP	Q10 = Q6g	leiomodoin-1	DQPA6	7	1.190E-4	3.03690E-5
VPRPP	Q11 = Q2a	SOX13	DQPA5	5	1.467E-4	5.24022E-5
PPPPL	Q12 = Q6a2	TSYL2	DQPA5	5	1.467E-4	5.24022E-5
PPGPQ	Q13	TOX2_HUMAN	DQPA5	5	1.968E-4	7.03124E-5
PVPPG	Q14	Annexin All	DQPA5	5	2.641E-4	9.43441E-5
PPxFPP	Q15	TG	DQPA5*	6	5.103E-4	1.51907E-4
RPxVEY	Q16	Ku70	DQPA5	6	5.103E-4	1.51907E-4
PPxLPxPP	Q17	CHD3	DQPA6	8	6.761E-4	1.50951E-4
GRPxxPPP	Q18	UBF1	DQPA6	8	9.072E-4	2.02543E-4
PPVxxVPP	Q19	ODP2	DQPA6*	8	9.072E-4	2.02543E-4
PxPPVE	Q20	CHD4	DQPA5	6	9.187E-4	2.73491E-4
PVXRPP	Q21	CHD4	DQPA5	6	9.187E-4	2.73491E-4
PPGFXP	Q22	Filamin-B	DQPA5*	6	9.187E-4	2.73491E-4
PxQxPVP	Q23	Annexin All	DQPA6*	8	1.217E-3	2.71769E-4
PVPxGF	Q24	SOX13	DQPA5*	6	1.233E-3	3.66966E-4
PPVXPV	Q25	PTPRN	DQPA5	6	1.233E-3	3.66966E-4
PSRXPP	Q26	TNR6A	DQPA5	6	1.233E-3	3.66966E-4
QLXQSI	Q27	Golgin 8A	DQPA5	6	1.654E-3	4.92389E-4
PPPXLG	Q28	AKA12	DQPA5	6	1.654E-3	4.92389E-4
PxPxxPVEY	Q29	SOX13	DQPA6*	9	2.067E-3	4.10237E-4
LxVNVVT	Q30	TG	DQPA5*	6	2.219E-3	6.60680E-4
PQXPXPXP	Q31	ODP2	DQPA6	9	2.774E-3	5.50449E-4
PPxxQxPVP	Q32	Annexin All	DQPA6-	9	3.722E-3	7.38584E-4
GxPxxPPPP	Q33	CHD3 + leiomodoin-1	DQPA6	9	4.994E-3	9.91020E-4
DQPA6 derivatives						
QxPVPRP	Q1a = Q34	cf. Q1 (SSA27)	DQPA6 only -*	7	1.190E-4	3.03690E-5
PxxPVPRP	Q1b = Q35		-	8	6.761E-4	1.50951E-4
PQxxVPRP	Q1c = Q36		-*	8	6.761E-4	1.50951E-4
PQxPxPRP	Q1d = Q37		*	8	5.039E-4	1.12500E-4
PQxPVxRP	Q1e = Q38			8	6.761E-4	1.50951E-4
PQxPVPxP	Q1f = Q39			8	6.761E-4	1.50951E-4
PQXPVPR	Q1g = Q40		-*	7	1.190E-4	3.03690E-5
PPPLxPxP	Q6a=Q7g=Q41	cf. Q6 and Q7 (CHD3)		8	6.761E-4	1.50951E-4
PxPPLxPxP	Q6b = Q42	cf. Q6 (CHD3)		9	3.722E-3	7.38584E-4
PPxPLxPxP	Q6c = Q43			9	3.722E-3	7.38584E-4
PPPxLxPxP	Q6d = Q44		-	9	3.722E-3	7.38584E-4
PPPPxxPxP	Q6e = Q45			9	2.774E-3	5.50449E-4
PPPLxLxxP	Q6f = Q46	CHD3 + TSYL2		9	3.722E-3	7.38584E-4
PPPLxP	Q6g = Q10	leiomodoin-1 + CHD3		7	1.190E-4	3.03690E-5
PPLxPxPP	Q7a = Q47	cf. Q7 (CHD3)		8	6.761E-4	1.50951E-4
PxPLxPxPP	Q7b = Q48		-	9	3.722E-3	7.38584E-4
PPxLxPxPP	Q7c = Q49		*	9	3.722E-3	7.38584E-4
PPPPxxPxPP	Q7d = Q50	CHD3+TSYL2		9	2.774E-3	5.50449E-4
PPPLxxPxPP	Q7e = Q51	cf. Q7 (CHD3)	*	9	3.722E-3	7.38584E-4
PPPLxPxxP	Q7f = Q52		-	9	3.722E-3	7.38584E-4
PPPLxPxP	Q7g=Q6a=Q41	cf. Q6 and Q7 (CHD3)		8	6.761E-4	1.50951E-4
PPVLPxP	Q8a = Q53	cf. Q8 (HMG TOX2)	-*	7	1.597E-4	4.07486E-5
PxxPVLxP	Q8b = Q54		-*	9	4.994E-3	9.91020E-4
PxPxxVLPxP	Q8c = Q55			9	4.994E-3	9.91020E-4
PxPPxLxP	Q8d = Q56			9	3.722E-3	7.38584E-4
PxPPVxPxP	Q8e = Q57		*	9	3.722E-3	7.38584E-4
PxPPVLxxP	Q8f = Q58			9	4.994E-3	9.91020E-4
PxPPVLP	Q8g = Q59		-	7	1.597E-4	4.07486E-5
Dense DQPA5 derivatives found by independent ScanProsite search and composing only fundamental DQPA						
PVPRP	Q1a2 = Q60	CHD4 + SSA27	DQPA5 only	5	1.467E-4	5.24022E-5
PPRVL	Q3a = Q61	cf. the first section of this table		5	1.968E-4	7.03124E-5
PRVLP	Q3b = Q62			5	1.968E-4	7.03124E-5
PPVLP	Q8a2 = Q63			5	1.968E-4	7.03124E-5
FPPGP	Q9a = Q64		*	5	1.467E-4	5.24022E-5
DQPA8 of window extend W=10 not included to our set of nonapeptide epitope related structures						
PPPLxPxPP	Q100	includes Q6 and Q7	DQPA8	10	9.570E-6	1.70932E-6

¹ Code of DQPA names. Order-related number of each DQPA is located after the Q character, forming order-related DQPA name. In addition to these order-related names, derivatives of fundamental DQPA are also associated with linkage-characterizing (LC) names. LC names are composed of i) order-related name of fundamental DQPA, which includes a sequence of given shorter derivative and ii) order character of such derivative (e.g. Q1b). In rare cases of two-times shortened derivatives, the numeral two terminates each LC name (e.g. Q8a2).

² number/1nro – though overall occurrence of DQPA identities in huAG sequences is higher than one, but only single occurrence is non-redundant when considering longer DQPA. For other abbreviations see Table 1.

³ DQPAⁿ – n means number of regular non-X DQPA; “-” denotes absence in Table WT2; * - absence in Table WT3.

⁴ All minimum Expect values (E_{min}) were lower than 0.005 (i.e. P < 0.005; cf. WP7). τ_i - values of Expect terms necessary for EDO enumeration (cf. section 2.5). L_i - DQPA length.

