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SHORT COMMUNICATION

Potential cross-reactivity between HPV16 L1 protein and sudden death-associated antigens

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In exploring the primary sequence of the human papilloma virus (HPV) 16 major capsid L1 protein for peptide sharing with human proteins, we find that 34 pentamers from the viral capsid protein are shared with human proteins that, when altered, have been linked to short QT syndrome, arrhythmogenic cardiac disorders, cardiovascular diseases and sudden death. In particular, nine out of the 34 viral pentamers are present in a human protein, titin, alterations of which have been linked to cardiac failure and sudden cardiac death. The present data may help evaluate the potential cross-reactivity risks in anti-tumor vaccination protocols based on HPV16 L1 protein.

Key words: HPV16 L1 protein; human proteome; cross-reactivity; anti-HPV16 vaccines; cardiovascular risk; sudden death

Reports from this laboratory showed that infectious agents have an unexpected, massive, and diffuse peptide overlapping throughout the entire human proteome at the penta-, hexa-, hepta, octa-, and nonapeptide level (1-4). The data are of crucial importance, especially considering that pentapeptides, eg, five amino acid motifs, can act as minimal biological units able to catalyze, regulate and determine fundamental cellular processes such as cell growth and apoptosis (5-7), hormone activity (8,9), depressive disorders and neuroprotection (10,11), oncoprotein expression (12-15), and immune recognition (16,17 and further references therein).

To gain a better understanding of the possible physiopathological aspects being involved in such a surprising peptide commonality between infectious agents and humans, we focus on qualitatively characterizing the peptide sharing by describing the human proteins harboring viral/bacterial peptides (18-20). The present study investigates the HPV16 L1-vs-human proteome overlap using pentapeptide modules as scanning probes and reports that HPV16 L1 matches occur in human proteins that, when altered, are associated with cardiovascular diseases and arrhythmogenic disorders.

HPV16 major capsid protein L1 (UniProtKB/Swiss-Prot P03101, VL1_HPV16) amino acid sequence was dissected into pentamers that were analyzed for exact matching to the human proteome using PIR perfect match program (pir.georgetown.edu/pirwww/) (21). The pentamers were offset by one residue, i.e, overlapped by four residues: MQVTF, QVTFI, VTFIY, TFIYI, etc. Functions and potential disease associations of the human proteins involved in the viral pentapeptide overlap were derived from the Universal Protein Resource (http://www.uniprot.org/) (22).

Table 1 shows that 34 HPV16 L1 pentamers occur in 23 human proteins that have been thoroughly studied at the (epi)genetic level in relation to diseases with cardiovascular involvement (23-36). Indeed, (epi)genetic alterations of the proteins listed in Table 1 may cause (or be associated with) diseases involving the heart or circulatory vessels such as hypertension, angina, atherosclerosis, coronary artery disease, myocardial infarction, heart failure, cerebrovascular diseases and

Table 1. Pentapeptide sharing between HPV16 L1 and human proteins involved in heart functions and metabolism

HPV16 L1: Aa Pos	Sequence	Human protein description[a]
31	LPSEA	**Q99959:** Plakophilin-2. PKP2. May play a role in junctional plaques. Defects in PKP2 are the cause of familial arrhythmogenic right ventricular dysplasia type 9. Characterized by partial degeneration of the myocardium of the right ventricle, electrical instability, and sudden death.
39	LPPVP	**MBNL1:** Muscleblind-like protein 1. Inhibits cardiac troponin-T pre-mRNA exon inclusion but induces insulin receptor pre-mRNA exon inclusion in muscle. Plays a role in the pathogenesis of dystrophia myotonica type 1, a muscular disorder characterized by myotonia, muscle wasting in the distal extremities, cataract, hypogonadism, male baldness and cardiac arrhythmias.
42	VPVSK	**O15273:** TELT. Telethonin. Titin cap protein. Muscle assembly regulating factor. Defects in TCAP are a cause of cardiomyopathy characterized by ventricular hypertrophy, which is usually asymmetric and often involves the interventricular septum. The symptoms include dyspnea, syncope, collapse, palpitations, and chest pain. They can be readily provoked by exercise. Malignant forms have high risk of cardiac failure and sudden cardiac death. Defects in TCAP are the cause of cardiomyopathy dilated type 1N, characterized by ventricular dilation and impaired systolic function, resulting in congestive heart failure, arrhythmia and a risk of premature death.
65	TSRLL	**Q8WZ42:** TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. Key component in the assembly and functioning of vertebrate striated muscles. Contributes to the fine balance of forces between the two halves of the sarcomere. Defects in TTN are the cause of: 1) hereditary myopathy with early respiratory failure (Edstrom myopathy); 2) cardiomyopathy familial hypertrophic type 9, characterized by ventricular hypertrophy. The symptoms include dyspnea, syncope, collapse, palpitations, and chest pain. They can be readily provoked by exercise. Malignant forms present a high risk of cardiac failure and sudden cardiac death; 3) cardiomyopathy dilated type 1G. Dilated cardiomyopathy is a disorder characterized by ventricular dilation and impaired systolic function, resulting in congestive heart failure and arrhythmia. Patients are at risk of premature death; 4) tardive tibial muscular dystrophy; also known as Udd myopathy. Muscle weakness and atrophy are usually confined to the anterior compartment of the lower leg. Clinical symptoms usually occur at age 35-45 years or much later; 5) limb-girdle muscular dystrophy type 2J, characterized by progressive weakness of the pelvic and shoulder girdle muscles. Severe disability is observed within 20 years of onset; 6) early-onset myopathy with fatal cardiomyopathy, a titinopathy that manifest typically from birth or infancy with hypotonia, muscle weakness, and delayed motor development.
90	KVSGL[b]	**Q8WZ42:** TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. See previous entry.
139	LGVGI	**P49748:** ACADV. Very long-chain specific acyl-CoA dehydrogenase, mitochondrial. VLCAD. Active toward esters of long-chain and very long chain fatty acids such as palmitoyl-CoA, mysritoyl-CoA and stearoyl-CoA. Defects in ACADV are the cause of very long chain acyl-CoA dehydrogenase deficiency, which leads to impaired long-chain fatty acid beta-oxidation. It is clinically heterogeneous, with three major phenotypes: a severe childhood form, with early onset, high mortality, and high incidence of cardiomyopathy; a milder childhood form, with later onset, usually with hypoketotic hypoglycemia as the main presenting feature, low mortality, and rare cardiomyopathy; and an adult form, with isolated skeletal muscle involvement, rhabdomyolysis, and myoglobinuria, usually triggered by exercise or fasting.
147	PLLNK	**P14923**: PLAK. Junction plakoglobin. JUP. Desmoplakin-3. Catenin gamma. Common junctional plaque protein. Defects in JUP are the cause of 1) Naxos disease, a disorder combining diffuse non-epidermolytic palmoplantar keratoderma with arrhythmogenic right ventricular dysplasia, cardiomyopathy and woolly hair; 2) familial arrhythmogenic right ventricular dysplasia type 12, characterized by degeneration of the myocardium of the right ventricle, electrical instability, and sudden death. Clinically defined by electrocardio-angiographic criteria. Pathologic findings, eg, replacement of ventricular myocardium with fatty and fibrous elements, preferentially involve the right ventricular free wall.

HPV16 L1: Aa Pos	Sequence	Human protein description[a]
198	GSPCT	**FBN1:** Fibrillin 1. Fibrillins are components of 10-12 nm extracellular calcium-binding microfibrils, which occur either in association with elastin or in elastin-free bundles. Defects in FBN1 are a cause of 1) Marfan syndrome (MFS), a disorder that affects the skeletal, ocular, and cardiovascular systems. Skeletal abnormalities occurring with MFS include scoliosis, chest wall deformity, tall stature, abnormal joint mobility. Ectopia lentis occurs in up to about 80% of MFS patients. The cause of premature death in MFS patients is progressive dilation of the aortic root and ascending aorta, causing aortic incompetence and dissection; 2) Weill-Marchesani, a rare connective tissue disorder characterized by short stature, brachydactyly, joint stiffness, and eye abnormalities including microspherophakia, ectopia lentis, severe myopia and glaucoma; 3) Shprintzen-Goldberg craniosynostosis syndrome, a rare syndrome characterized by a marfanoid habitus, craniosynostosis, characteristic dysmorphic facial features, skeletal and cardiovascular abnormalities, mental retardation, developmental delay and learning disabilities; 4) MASS syndrome, characterized by involvement of the Mitral valve, Aorta, Skeleton and Skin.
244	SEVPL	**Q8WZ42:** TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. See previous entry.
266	EPYGD	**P14923:** PLAK. Junction plakoglobin. Desmoplakin-3. Catenin gamma. See previous entry.
290	AGAVG	**P11310:** ACADM. Medium-chain specific acyl-CoA dehydrogenase, mitochondrial. Defects in ACADM are the cause of medium-chain acyl-CoA dehydrogenase deficiency. It is an autosomal recessive disease which causes fasting hypoglycemia, hepatic dysfunction, and encephalopathy, often resulting in death in infancy. The disease frequency is one in 13000. Defects in ACADM may cause sudden neonatal death.
293	VGENV	**Q8WZ42:** TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. See previous entry.
305	GSGST	**JAG1:** Protein jagged-1. Ligand for multiple Notch receptors and involved in the mediation of Notch signaling. May be involved in cell-fate decisions during hematopoiesis. Seems to be involved in early and late stages of mammalian cardiovascular development. Expressed in 32-52 days embryos in the distal cardiac outflow tract and pulmonary artery, major arteries, portal vein, and in the neural tube. Defects in JAG1 are the cause of 1) Alagille syndrome type 1, a multisystem disorder defined clinically by hepatic bile duct paucity and cholestasis in association with cardiac, skeletal, ophthalmologic manifestations, and characteristic facial features; 2) tetralogy of Fallot, a congenital heart anomaly which consists of pulmonary stenosis, ventricular septal defect, dextroposition of the aorta (aorta is on the right side instead of the left) and hypertrophy of the right ventricle. This condition results in a blue baby at birth due to inadequate oxygenation.
308	STANL	**Q8WZ42:** TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. See previous entry.
359	VVDTT[c]	**Q8WZ42:** TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. See previous entry.
361	DTTRS	**Q8WZ42**: TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. See previous entry.
375	STSET	**P55084:** ECHB. Trifunctional enzyme subunit beta, mitochondrial. Enzyme activities: 3-ketoacyl-CoA thiolase, acetyl-CoA acyltransferase, and beta-ketothiolase. HADHB. Defects in HADHB are a cause of trifunctional protein deficiency, biochemically defined by the loss of all three enzyme activities. Clinical manifestations include hypoglycemia, cardiomyopathy and sudden death.
431	GLQPP	**RYR1:** Ryanodine receptor 1. Present in skeletal muscle, cerebellum and hippocampus. Defects in RYR1 are the cause of 1) malignant hyperthermia susceptibility type 1, a main causes of death due to anesthesia, with contractures, metabolic acidosis, tachycardia and death; 2) central core disease, a condition that produces the 'floppy infant', with neonatal hypotonia, delayed motor development, muscle weakness and amyotrophy.

Table 1. Continued

HPV16 L1: Aa Pos	Sequence	Human protein description[a]
432	LQPPP	**NOTC1:** Neurogenic locus notch homolog protein 1. NOTCH1. In altered form, may contribute to transformation or progression in some T-cell neoplasms. Defects in NOTCH1 are a cause of bicuspid aortic valve. A common defect in the aortic valve in which two rather than three leaflets are present. It is often associated with aortic valve calcification and insufficiency. In extreme cases, the blood flow may be so restricted that the left ventricle fails to grow, resulting in hypoplastic left heart syndrome. **FEV:** Protein FEV (Fifth Ewing Variant protein). Functions in the differentiation and the maintenance of the central serotonergic neurons. Defects in FEV may be associated with susceptibility to sudden infant death syndrome.
433	QPPPG	**FEV:** Protein FEV (Fifth Ewing variant protein). See previous entry.
434	PPPGG	**MEF2A:** Myocyte-specific enhancer factor 2A. Transcriptional activator. Mediates cellular functions in skeletal and cardiac muscle development, and also in neuronal differentiation and survival. Defects in MEF2A might be a cause of autosomal dominant coronary artery disease 1 with myocardial infarction.
438	GTLED	**P13533:** MYH6. Myosin heavy chain, cardiac muscle alpha isoform. Function: muscle contraction. Defects in MYH6 are a cause of cardiomyopathy familial hypertrophic, a disorder characterized by ventricular hypertrophy, which is usually asymmetric. The symptoms (dyspnea, syncope, collapse, palpitations, and chest pain) can be readily provoked by exercise. Malignant forms present high risk of cardiac failure and sudden cardiac death. **P12883:** MYH7. Myosin heavy chain, cardiac muscle beta isoform. Function: muscle contraction. Defects in MYH7 are the cause of 1) cardiomyopathy familial hypertrophic type 1, characterized by ventricular hypertrophy, which is usually asymmetric and often involves the interventricular septum. The symptoms (dyspnea, syncope, collapse, palpitations, and chest pain) can be readily provoked by exercise. Malignant forms present high risk of cardiac failure and sudden cardiac death; 2) myosin storage myopathy; 3) scapuloperoneal myopathy MYH7-related, a progressive muscular atrophia beginning in the lower legs and affecting the shoulder region earlier and more severely than distal arm; 4) cardiomyopathy dilated type 1S, characterized by ventricular dilation and impaired systolic function, resulting in congestive heart failure, arrhythmia and a risk of premature death.
449	SQAIA	**P15924:** DESP. Desmoplakin. DP. 250/210 kDa paraneoplastic pemphigus antigen. DSP. Major high molecular weight protein of desmosomes. Involved in the organization of the desmosomal cadherin-plakoglobin complexes and in the anchoring of intermediate filaments to the desmosomes. Defects in DSP are the cause of: 1) palmoplantar keratoderma striate type 2, characterized by skin thickening in the palms (linear pattern) and the soles (island-like pattern) and flexor aspect of the fingers; 2) cardiomyopathy dilated with woolly hair and keratoderma; also known as Carvajal syndrome, it is characterized by a generalized striate keratoderma particularly affecting the palmoplantar epidermis, woolly hair, and dilated left ventricular cardiomyopathy; 3) familial arrhythmogenic right ventricular dysplasia type 8, characterized by partial degeneration of the myocardium of the right ventricle, electrical instability, and sudden death. Clinically defined by electrocardiographic criteria. Pathologic findings, eg, replacement of ventricular myocardium with fatty and fibrous elements, preferentially involve the right ventricular free wall; 4) skin fragility-woolly hair syndrome, characterized by focal palmoplantar keratoderma, hyperkeratotic plaques on the trunk and limbs, and woolly hair with varying degrees of alopecia; 5) epidermolysis bullosa lethal acantholytic characterized by severe fragility of skin and mucous membranes. The phenotype is lethal in the neonatal period because of immense transcutaneous fluid loss. Typical features include universal alopecia, neonatal teeth, and nail loss.
457	HTPPA	**IRS1:** Insulin receptor substrate 1. May mediate the control of various cellular processes by insulin. IRS1 Arg-971 polymorphism impairs the ability of insulin to stimulate glucose transport, glucose transporter translocation and contributes to the risk for atherosclerotic cardiovascular diseases associated with non-insulin-dependent diabetes mellitus by producing a cluster of insulin resistance-related metabolic abnormalities.

HPV16 L1: Aa Pos	Sequence	Human protein description[a]
468	KKYTF	**Q8WZ42:** TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. See previous entry.
475	VNLKE	**Q02487:** DSC2. Desmocollin-2. Component of intercellular desmosome junctions. Defects in DSC2 are the cause of familial arrhythmogenic right ventricular dysplasia (ARVD) type 11. ARVD is characterized by partial degeneration of the myocardium of the right ventricle, electrical instability, and sudden death. It is clinically defined by electrocardiographic criteria. Pathologic findings, eg, replacement of ventricular myocardium with fatty and fibrous elements, preferentially involve the right ventricular free wall.
479	EKFSA	**DICER:** Endoribonuclease. Required for formation of the RNA induced silencing complex. Targeted deletion of Dicer in the heart leads to dilated cardiomyopathy and heart failure.
492	RKFLL	**DICER:** Endoribonuclease. See previous entry.
495	LLQAG	**NODAL:** Essential for mesoderm formation and axial patterning during embryonic development. Defects in NODAL are the cause of visceral heterotaxy autosomal type 5, a complex disorder due to disruption of the normal left-right asymmetry of the thoracoabdominal organs. Clinical features include situs inversus viscerum, transposition of the great vessels, ventricular septal defect, atrial septal defect, and dextrocardia.
496	LQAGL	**Q13936:** CAC1C. Voltage-dependent L-type calcium channel subunit alpha-1C. CACNA1C. Defects in CACNA1C are the cause of 1) Timothy syndrome, a disorder characterized by multiorgan dysfunction including lethal arrhythmias, webbing of fingers and toes, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities and autism; 2) Brugada syndrome type 3, a heart disease characterized by the association of Brugada syndrome with shortened QT intervals. Brugada syndrome is a tachyarrhythmia characterized by right bundle branch block and ST segment elevation on an electrocardiogram. It can cause the ventricles to beat so fast that the blood is prevented from circulating efficiently in the body.
498	AGLKA	**Q8WZ42:** TTN. Titin. Connectin. Rhabdomyosarcoma antigen MU-RMS-40.14. See previous entry.
518	SSTST	**Q9BTV4:** TMM43. Transmembrane protein 43. Protein LUMA. TMEM43 . Defects in TMEM43 are the cause of familial arrhythmogenic right ventricular dysplasia (ARVD) type 5. ARVD is characterized by partial degeneration of the myocardium of the right ventricle, electrical instability, and sudden death.
524	AKRKK	**P15924:** DESP. Desmoplakin. DP. 250/210 kDa paraneoplastic pemphigus antigen. See previous entry.
527	KKRKL	**P13533:** MYH6. Myosin heavy chain, cardiac muscle alpha isoform. See previous entry. **P12883:** MYH7. Myosin heavy chain, cardiac muscle beta isoform. See previous entry.

[a]UniProt/Swissprot accession number in boldface. For further details and references, visit www.uniprot.org.
[b]HPV16 $L1_{90\text{-}94}$KVSGL occurs three times.
[c]HPV16 $L1_{359\text{-}363}$VVDTT occurs twice.

accident (stroke), arrhythmia, cardiac valve diseases, peripheral vascular diseases such as obstructions of large arteries in the arms and legs, and sudden death. Eg, the viral-vs-human overlap involves:

- components of intercellular desmosome junctions such as plakophilin-2, desmoplakins, and desmocollin-2. Defects in these desmosomal proteins have been reported in arrhythmogenic right ventricular cardiomyopathy (23-25);
- titin, a crucial protein for myofibrillar elasticity and integrity, variants of which are the molecular basis for dilated cardiomyopathy (26-28). Twelve viral pentapeptides (including multiple occurrences) are present in titin, with $L1_{90\text{-}94}$KVSGL and $L1_{359\text{-}363}$ VVDTT occurring more than once (see Table 1);
- MYH6 and MYH7, i.e. two isoforms of the myosin heavy chain that are specifically located in the cardiac muscle. When altered, MYH6 and MYH7 may be the cause of congestive heart failure and sudden

cardiac death (29-32). Table 1 shows that two different viral pentapeptides occur in each of the two myosin heavy chain isoforms;

- voltage-dependent L-type calcium channel subunit alpha-1C (CAC1C) (33), alterations of which are the cause of: 1) Timothy syndrome, a disorder characterized by multiorgan dysfunction including lethal arrhythmias (34), and 2) Brugada syndrome type 3, a heart disease characterized by the association of Brugada syndrome with shortened QT intervals (35). Brugada syndrome is a tachyarrhythmia characterized by right bundle branch block and ST segment elevation on an electrocardiogram. It can cause ventricular fibrillation (i.e. the ventricles beat so fast that the blood is prevented from circulating efficiently in the body). When this situation occurs, the individual will faint and may die in a few minutes if the heart is not reset;
- ryanodine receptor 1, a protein involved in malignant hyperthermia susceptibility type 1 (a main causes of death due to anesthesia, with contractures, metabolic acidosis, tachycardia and death), and central core disease (a condition that produces the 'floppy infant', with neonatal hypotonia, delayed motor development, muscle weakness and amyotrophy) (36).

Almost constantly, physical exercise triggers the fatal cardiac myopathies linked to alterations of telethonin, titin, mitochondrial acyl-CoA dehydrogenase, MYH6, and MYH7 proteins.

CONCLUSION

The present communication not only confirms and extends previous reports describing a high level of perfect peptide matching between bacterial/viral antigens and the human proteome (1-4), but also suggests that possible immune cross-reactions deriving from utilization of HPV L1 in vaccination might be a source of cardiac implications. Thus, the present data add to our previous reports in underlining that a thorough understanding of potential antigen cross-reactivity is vitally important for the successful development and application of vaccination protocols (37-41). Failure to analyze and minimise levels of cross-reactivity might lead to harmful, even lethal, events.

DISCLOSURE

The author reports no conflicts of interest in this work.

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