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Molecular Genetics of Inherited Cardiac Conduction Defects in Humans and Dogs

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Abstract : Heart diseases related to conduction system can be occurred by primary defects in conduction system and by secondary to morphological heart diseases or drug toxicities. Multiple molecular defects responsible for arrhythmogenesis, including mutations in ion channels, cytoplasmic ion-channel-interacting proteins, gap-junction proteins, transcription factors and a kinase subunit, were found to be associated with the aetiology of primary cardiac conduction defects, especially inherited form. Despite a big progress in unveiling human arrhythmogenesis, conduction defects in dog has not been well studied except sudden death syndrome in German shepherd. In this review, molecular genetics in cardiac arrhythmogenesis, inherited human diseases associated with conduction defects and similar diseases in dogs will be discussed.

Key words **:** Long-QT syndrome, Sudden death syndrome, Inherited conduction defect, Ion channel disease, Cardiac arrhythmogenesis

Introduction

Cardiac conduction defects, so called cardiac arrhythmias, can be divided into primary or secondary. Primary cardiac arrhythmias are mainly due to genetic defects such as mutated genes associated with ion channel and cardiac transcription factors. Acquired arrhythmias are mainly due to hypertrophic heart diseases related to heart failure caused by chronic coronary artery disease, cardiomyopathy or other forms of cardiac injury. Cardiac conduction defects can be initiated by environmental risk factors (e.g. serum Na-K imbalance) and certain drugs (e.g. digitalis toxicities). However, the mechanisms of arrhythmogenesis are complicated and still not clearly known[22] despite recent advances in human molecular genetics related to understanding the mechanisms of cardiac arrhythmogenesis[35,58].

Regardless of causes of initiation, the cardiac arrhythmias are maintained and propagated by re-entrant circuits which is formed by abnormal repolarization or conduction (Fig 1). Mutations in ion-channel genes (*KVLQT1*, *HERG*, *SCN5A*, *minK*, *MiRP1* and *Kir2.1*) or in the channel-interacting-protein gene (*KChIP2*) directly affect the current fluxes that mediate action potentials, and this can increase dispersion of repolarization and lead to the formation of functional re-entry circuits. A prolonged QT interval, the appearance of a J or U wave and polymorphic ventricular tachycardia (*torsade de pointes*) without AV block or conduction delay are characteristically noticed in diseases associated with genetic defects in those genes. The cardiac conduction defects can be also occurred by mutations in genes encoding gap-junction proteins (*Cx40* and *Cx43*), and genes encoding transcription factors (*Nkx2.5* and *Tbx5*). The disruption of gap junctions results in cell uncoupling and leads to the formation of anatomical re-entry circuits. Unlike above described defects, an AV block or a widening of QRS duration due to a decreased conduction velocity with localized conduction delay is characteristic in these diseases. The ventricular tachycardias in these diseases are usually monomorphic so that they are less malignant. Some conduction diseases can affect both repolarization and conduction (e.g. Brugada syndrome) possibly by malicious effect on *Cx40* and slow outward delayed-rectifier potassium current (I_{Ks}).

As discussed above, the cardiac conduction defects are multifactorial defects influenced by genetic and environmental factors. Furthermore each affected individual can have different degree of risk factors depending on genetic background and environmental risk. One of advantage in canine genetic is that dog has less variable phenotypic expressivity. In other word, in human population, certain genetic diseases can have highly variable phenotype due to genetic heterogeneity (genetic remixing) and different degree of penetrance. However, pure breed dogs will have the higher chance that disease phenotype inherited through generations to generations by intentional inbreeding to maintain the purity of breed. Therefore, they may have the more invariable form of disease phenotype, although there will be a variance in phenotype in different breeds of dog. Therefore, canine model would be a better animal model for human genetic diseases, especially phenotypically varied.

Despite this advantage of canine model, conduction defects in dog has been poorly studied except sudden death syndrome in German shepherd. Therefore, in this review, molecular genetics in cardiac arrhythmogenesis, and inherited human diseases associated with these defects will be discussed. Furthermore, the inherited conduction defects in dogs and their possible model for human inherited conduction defects will be discussed.

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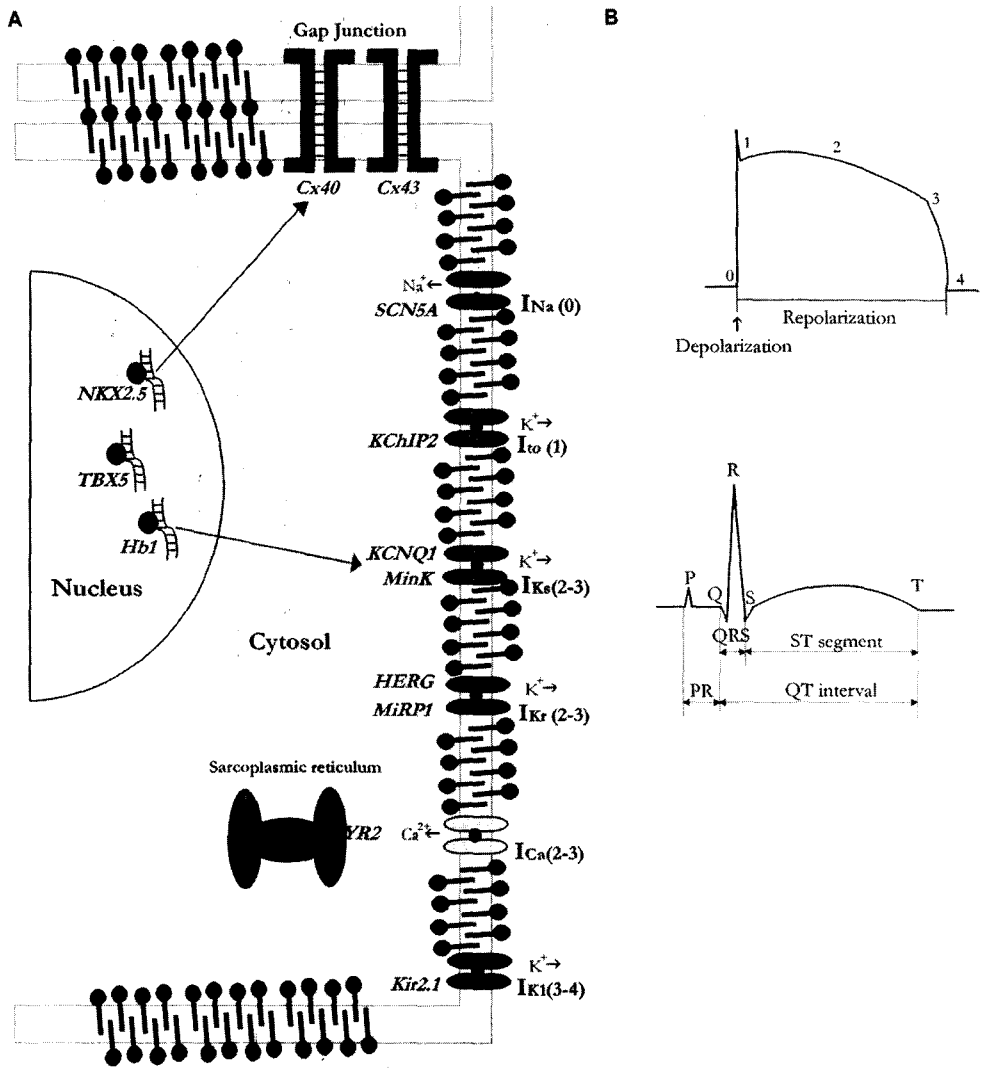

Fig 1. Genes responsible for cardiac arrhythmogenesis (A) and cardiac action potential with respect to electrocardiogram (B). Several ion channels are involved in the generation of cardiac action potential. Any defects regulating this action potential can cause conduction disturbances including prolongation PR interval, atrioventricular block and QRS widening and repolarization disturbances including prolongation QT interval. *Cx*, connexin; I_{Ca}, inward calcium current, I_{Kr}, rapid outward delayed-rectifier potassium current; I_{Ks} slow outward delayed-rectifier potassium current; I_{Na}, inward sodium current; I_{to}, transient outward potassium current, *KChP2*, voltage-gated-potassium-channel-interacting protein 2; *MiRP1*, minK-related protein1; *RYR2*, ryanodine receptor 2.

Molecular genetics in cardiac arrhythmogenesis

Several genes associated human familial cardiac arrhythmogenesis and their pathways involved in arrhythmogenesis have recently been identified. Those genes can be categorised into 5 groups based on their function; i) genes affecting ion-channel, ii) a gene encoding a cytoplasmic channel-interacting protein, iii) genes associated with gap-junction, iv) transcription factors, v) a gene encoding the 2 subunit of the AMP-activated protein kinase.

Group 1: Genes affecting the function of ion channels

Series of changes in ion channels across the cell membrane mediate the depolarization and repolarization of cardiomyocytes. Mutations in various ion-channel genes are responsible for human familial long Q-T syndromes and sudden death syndromes including Brugada disease.

KVLQT1 (also known as *KCNQ1*) encodes a potassium channel subunit and mediates slowly activating delayed-rectifier K^+ current (I_{Ks}). It is also involved in controlling the repolarization of cardiac action potentials[4,45]. Mutations on this gene are responsible for up to 45% of Long-QT syndrome in human and lead to a reduction in repolarizing potassium currents and a subsequent delay in the repolarization of the myocytes due to disturbances in channel function.

HERG (also known as *KCNH2*) encodes another type of

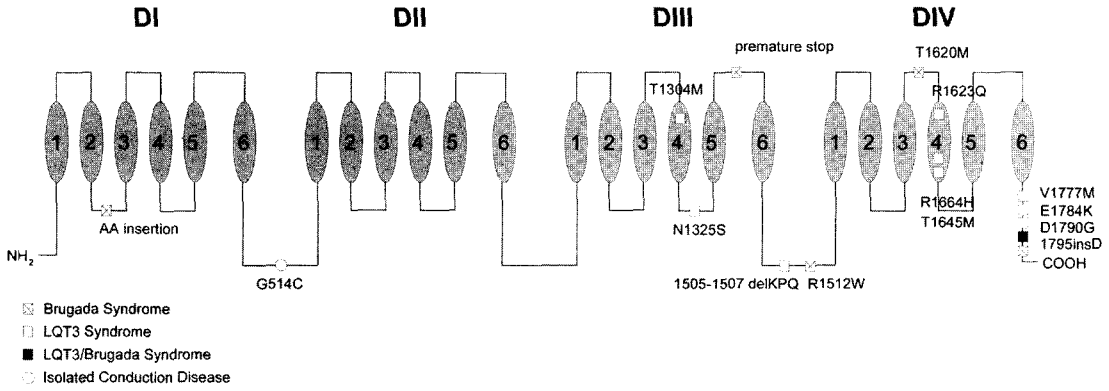

Fig 2. The loci of inherited *SCN5A* mutations that modify sodium channel function. The phenotype of disease varied by the location of mutation on sodium channel gene.

potassium channel subunit and mediates rapidly activating delayed-rectifier K^+ current (I_{Kr}). With I_{Ks}, it is also involved in controlling the repolarization of cardiac action potentials (Fig 1). Up to 40% of human Long-QT patients have a defect in *HERG*. Delayed process of repolarization is a major outcome of this mutation. This mutation has a variable degree of penetrance and can be predisposed by other factors such as drugs[42].

SCN5A encodes a sodium channel subunit and is responsible for myocellular depolarization. Mutations on this gene are also responsible for up to 7% of cases of inherited Long-QT syndrome, as well as Brugada syndrome[53]. Disease phenotype can be varied by location and type of mutation (Fig 2). In gain-of-function mutations, prolonged action potentials caused by abnormal maintenance of the depolarizing current is the main cause of pathogenesis[60] but in a loss-of-function mutation, a reduction in the density of functional sodium channels and a slower conduction velocity in myocytes are involved in pathogenesis[37].

MinK (also known as *KCNE1*) encodes a potassium channel accessory subunit and mediates I_{Ks} by interaction with *KVLQT1*. Mutations in *MinK* are responsible for up to 5% of inherited Long-QT syndromes and affect the repolarization process of cardiomyocyte.

MiRP1 (also known as *KCNE2*) encodes another type of potassium channel accessory subunit and mediates I_{Kr} by interaction with *HERG*. Loss-of-function mutations in *MiRP1* prolong action-potential duration by inhibiting I_{Kr}.

Kir2.1 (also known as *KCNJ2*) encodes a potassium channel subunit and mediates the inward-rectifier K^+ current (I_{K1}). It is involved in controlling the resting membrane potential and the final part of repolarization. The mutations in this gene are responsible for Andersen's syndrome[10,39] and possibly inhibit I_{K1} through a dominant-negative effect[41].

RyR2 encodes the cardiac ryanodine receptor and is involved in calcium release in ion channel. Furthermore, it is responsible for human familial polymorphic ventricular tachycardia. An elevation in catecholamine levels during stimulation of the sympathetic nervous system can lead to a calcium leak from the SR (sarcoplasmic reticulum) during diastole, possibly generating delayed afterdepolarizations (DADs) and triggering fatal cardiac arrhythmias[27].

Group 2: Cytoplasmic channel-interacting protein gene

KChIP2 (Potassium-channel-interacting protein 2 gene) encodes three cytoplasmic accessory proteins for the Kv4.2 and Kv4.3 channels, mediates the transient outward K^+ current (I_{to}) and regulates the surface expression and gating properties of these channels[3]. As it is responsible for generating the early repolarization of action potentials, it may be involved in the pathogenesis of polymorphic ventricular tarchycardia (*torsade de pointes*). In mouse knockout study, the *KChIP2* deficient mice have a higher susceptibility to malignant ventricular arrhythmias[24].

Group 3: Defects in gap-junction proteins

Because intercellular gap junctions help the conduction of electrical impulses throughout the myocardium, any mutations on the genes maintaining gap junction can be responsible for cardiac conduction defects. Three different types of connexin (Cx) protein, Cx40, Cx43 and Cx45 were found in the gap-junction channels of mammalian heart[10,59]. Current mouse model study showed *Cx40* and *Cx43* are involved in conduction defects.

Cx40 is expressed in atria and the conduction tissues except the AV node. *Cx40* knockout mice exhibit multiple abnormalities in the atria and in the central conduction system due to impairment in the SA (sinoatrial), intra-atrial and AV (atrioventricular) conduction properties[51].

Cx43 is expressed in all atrial and ventricular myocytes except main conduction tissues in all developmental stages.[10] *Cx43* knockout mice exhibit severe developmental defects and spontaneous ventricular tachycardia which is responsible for sudden cardiac death. Loss of *Cx43* gap-junction channels can generate ectopic impulse and early afterdepolarizations which leads to arrhythmias. Cardiac arrhythmias can be also induced by an increased anisotropic conduction which is prone to form an unidirectional block and re-entry circuits.

Group 4: Defects in transcription factors

Cardiac transcription factors involved in the specification and differentiation of the conduction-system are also responsible for certain forms of inherited and familial human conduction defects.

HF-1b (a member of the SP-1 transcription-factor gene family) is preferentially expressed in the cardiac conduction system and in ventricular myocytes. It is involved in the regulation of the transition between the myogenic and conduction-system cell lineages[61]. *HF-1b* deficient mice show conduction-system defects, including spontaneous ventricular tachycardia, AV block display and sudden cardiac death[36]. The absence of *HF-1b* may affect the transition between the myocyte and conduction-system cell lineages and thus lead to defects in both lineages and cause arrhythmias.

Nkx2.5 (a homeobox transcription factor) is an important gene in early cardiac development, interacts with other cardiac transcription factors including *TBX5, TBX20, GATA4* and *GATA5* and regulates the expression of many downstream cardiac genes, including *e-Hand, Cx40* and the atrial natriuretic factor (*ANF*) gene. Furthermore *Nkx2.5* may be involved in the maturation and maintenance of AV-node function throughout life and thus defect in *NKX2.5* gene can be responsible for AV block[21]. Several autosomal dominant congenital heart diseases (e.g. atrial septal defects, ventricular septal defects, tetralogy of Fallot, AV conduction delays) were associated with mutations on this gene[6,47].

Tbx5 (a T-box transcription-factor gene family) is an important gene in vertebrate tissue patterning and differentiation and the development of a functional cardiac conduction system. It can directly interact with *Nkx2.5* and thus can regulate the downstream genes such as *ANF* and *Cx40*. Mutations on *Tbx5* is responsible for human Holt-Oram syndrome. AV block is a main conduction defect seen in patients with Holt-Oram syndrome.

Group 5: Defects in kinase subunits

PRKAG2 (a AMP-activated protein kinase; AMPK) is a subunit of AMP-activated protein kinase and this subunit contains an AMP binding site. The mutations on *PRKAG2* are responsible for human Wolff-Parkinson-White syndrome, which is characterized by ventricular pre-excitation, tachyarrhythmias and progressive conduction defects with or without hypertrophic cardiac diseases.[12,13] Although the arrhythmogenic mechanisms by *PRKAG2* mutations has not been clearly identified, a decreased ion-channel activity and sarcomeric contraction, the formation of accessory AV fibers and dysregulation of ion channels suggested to be responsible for the pathogenesis[12-14].

Inherited conduction defects in human

Long QT Syndrome

Long QT syndrome is characterized by malignant ventricular arrhythmias and syncopes due to by prolongation of the QT interval associated with abnormal repolarization process (Fig 3)[26]. Two different forms of inherited long QT syndrome have been reported. Jervell and Lange-Nielsen syndrome (JLNS) is autosomal-recessive disease and is often associated with congenital deafness[20,26]. Romano-Ward syndrome (RWS) is autosomal-dominant disease but is not associated with deafness. RWS is more common form in human Long-QT syndrome. Seven genes, which are associated with ion channels controlling automaticity of electrical activity in the cardiac cells, were found to be responsible for inherited long QT syndrome in human. The Long-QT genes are identified by an LQT number that reflects the chronological order in which the LQTS gene locus was discovered and by the name of the mutated gene that has been linked to Long-QT syndrome (Table 1). Currently, more than 150 different mutations have been identified in 7 LQTS genes, with LQT1 (43%), LQT2 (45%), and LQT3 (7%) accounting for 95% of the identified mutations[52]. The Long-QT is considered as an ion-channel disease and any mutations on those genes can modify the cardiac action potential and voltage gradient in the conduction tissues, especially in the ventricular level, which is responsible for reentrant arrhythmias. This variability in expression in related individuals with the same mutation suggests the influence of environmental factors and/or the presence of other genetic effects. The electrocardiogram shows sinus bradycardia with prolongation of the corrected QT inter-

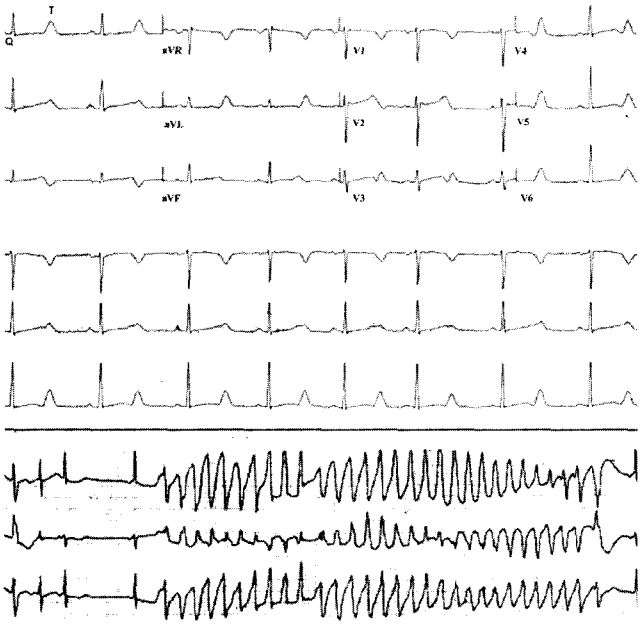

Fig 3. Human Long QT syndrome. A: Twelve-lead electrocardiogram from a patient with Long QT syndrome (HR:48/min, QT interval: 0.68s, QTc: 0.61s). This patient has a prominent T wave and long ST-segment. B: The short-long-short sequence before the onset of *torsade de pointes* in a patient with Long-QT syndrome.

Table 1. Molecular defects associated with cardiac conduction disturbances. Molecular mechanisms for cardiac conduction defects are mainly caused by either delayed repolarization process (e.g. prolonged QT interval) or conduction block (e.g. prolonged PR interval, widening QRS, AV block), depending on physiological function of defective genes

Inheritance	Disease	Locus	Gene	Target defected	Mechanism
AD, AR	LQT, TdP	11p5.5	KCQNQ1 (LQT1)	Potassium channel, I_{Ks}	Repolarization
AD	LQT	7q35-36	HERG (LQT2)	Potassium channel, I_{Kr}	Repolarization
AD	Brugada, LLD	3p21-24	SCN5A (LQT3)	Sodium channel, I_{Na}	Both
AD	LQT	4q25-27	Ankyrin B (LQT4)	?	Repolarization
AD, AR	LQT	21q22.1	Mink (LQT5)	Potassium channel, I_{Ks}	Repolarization
AD	LQT	21q22	MiRP1 (LQT6)	Potassium channel, I_{Kr}	Repolarization
AD	Anderson	17q23	KCNJ2 (LQT7)	Potassium channel, $I_{Kir2.1}$	Repolarization
AD	ARVD, C-PMVT	1q42	RYR2	Calcium channel	Conduction
AD	SPVT	9q34	KChIP2*	Channel interaction, I_{to}	Conduction
AR	ND	17q21	Plakoglobin	Intercellular junction	Conduction
AD	AVB, AT	1q21	Cx 40*	Gap junction	Conduction
AD	VT, SCD	6q21	Cx 43*	Gap junction	Conduction
AD	AVB, VT	12	HF-1b*	Cardiomorphogenesis	Both
AD	ASD, VSD, ToF, AVB	5q34	NKX2.5	Cardiomorphogenesis	Conduction
AD	Holt-Oram	12q24	TBX5	Cardiomorphogenesis	Conduction
AD	AVB, WPW, AF, HCM	7q35	PRKAG2	Kinase subunit	Conduction

AD: Autosomal dominant, AR: Autosomal recessive, LQT: Long-QT syndrome, TdP: Torsade de ponites, Brugada: Brugada syndrome, LLD: Lenergre-Lev disease, Anderson: Andersons syndrome, ARVD: Arrhythmogenic right ventricular dysplasia, C-PMVT: Catecholaminergic polymorphic ventricular tachycardia, SPVT: Sustained polymorphic ventricular tachycardia, ND: Naxos disease, AVB: Atrioventricular block, AT: Atrial tachycardia, VT: ventricular tachycardia, ASD: Atrial septal defect, VSD: Ventricular septal defect, ToF: Tetralogy of Fallot, WPW: Wolff-Parkinson-White syndrome, AF: Atrial fibrillation, HCM:Hypertrophic cardiomyopathy, I_{Ks}:Slowly activating delayed-rectifier K^+ current, I_{Kr}:Rapidly activating delayed-rectifier K^+ current, $I_{Kir2.1}$: Inward-rectifier K^+ current, I_{Na}: Sodium current, I_{to}: Transient outward K^+ current *Abnormalities were only noticed in experimental mouse studies.

val (QTc). The long ST-segment interval before the onset of a late, prominent T wave is characteristic of the LQT3 genotype. The clinical course of patients with LQTS is variable and is influenced by genotype, sex, environmental factors, and therapy[34].

Brugada Syndrome

The Brugada syndrome is an autosomal dominant arrhythmogenic disease accounted for sudden cardiac death in human[5]. Recent studies indicate that unexplained sudden death syndrome, prevalent in southeast Asia (e.g. *bangungu* in the Philippine, *lai tai* in Thailand; unexpected death of young adults during sleep) and Brugada syndrome are phenotypically, genetically, and functionally the same disorder.

Several dozen mutations on *SCN5A* (the subunit of the cardiac sodium channel gene) are responsible for this syndromes (Fig 2)[30]. The pathogenesis accounted for this syndrome are (1) failure of the sodium channel to express; (2) reduced current due to a shift in the voltage and time dependence of sodium channel current (I_{Na}) activation, inactivation, or reactivation; or (3) reduced contribution of I_{Na} during the early phases of the action potential resulting from accelerated inactivation of the sodium channel.

The most typical electrocardiographic features of the Brugada syndrome are: (1) an accentuated J wave appearing principally in the right precordial leads (V1 to V3) and taking the form of an ST-segment elevation, often followed by a negative T wave; (2) very closely coupled extrasystoles; and (3) rapid polymorphic VT, which at times may be indistinguishable from ventricular fibrillation (VF). The ST-segment elevation may also display a saddleback appearance[7], and VT in rare cases may be monomorphic.

Brugada syndromes are also quite similar to other form of familial arrhythmogenic diseases but it is quite distinct from the genetic standpoint; the Brugada syndrome has thus far been linked only to mutations in *SCN5A*, whereas arrhythmogenic RV dysplasia (ARVD) has been linked to seven different chromosomal sites and three putative genes.

Familial Polymorphic Ventricular Tachycardia

Calcium plays an important role in electrical conduction and contractile function of the heart implying that any defects in protein interacting calcium can cause conduction defects and cardiomyopathy. Ryanodine receptors located in the sarcoplasmic reticulum of cardiomyocyte and involved in efflux of calcium into cytoplasm. Mutations on *RYR2* (ryanodine receptor 2) is associated with two different diseases, arrhythmogenic right ventricular dysplasia (ARVD)[40] and catecholaminergic polymorphic ventricular tachycardia (C-PMVT)[57]. Although most features of both diseases are similar (even the same genetic aetiology), distinct difference is that ARVD is accompanied by structural abnormalities whereas C-PMVT is

not. Roles of genetic modifiers, or some other environmental modifiers are possibly important for the pathogenesis of these diseases.

Catecholaminergic Polymorphic VT. It is an autosomal-dominant inherited disease with a mortality rate of 30% by the age of 30 years. Phenotypically, it is characterised by polymorphic ventricular extrasystoles and tachycardia during exercise or stress which progress to *torsade de pointes* and sudden cardiac death, without any structural evidence of myocardial disease. *RYR2* is implicated in this disease. Another gene *CASQ2* (calsequestrin gene; internal constituent of SR) has been recently identified and seems to play a role in pathogenesis of this disease[40,57].

Arrhythmogenic right ventricular dysplasia (ARVD). It is a common cause of sudden cardiac death (~17% of sudden death in the young in USA) and is characterized by fatty infiltration of the right ventricle, fibrosis and ultimately thinning of the wall with chamber dilatation[11,50,54,55]. Several genetic loci associated with this disease have been reported [2,25,28,38,44,49], but recently, a responsible gene was found to be *RYR2*[57]. In ECG, patients showed an inverted T waves in the right precordial leads, late potentials and right ventricular arrhythmias with left branch bundle block (LBBB). It is difficult to make a diagnosis, because the first sign of this disease is often sudden death and the lesion is confined to the free wall of right ventricle (inaccessibility for biopsy)[27].

Other inherited conduction defects

Lenergre-Lev disease. It is characterized by progressive cardiac conduction defects and causes continuous alteration of cardiac conduction through His bundle and Purkinje system. In ECG, patients show right and left branch bundle block and widening QRS and progress to complete atrioventricular block. Mutation on *SCN5A* is also responsible for this disease[46].

Naxos disease (ND). It is an autosomal recessively inherited disorder characterized by cardiac conduction defects (ventricular tachycardia with inversion of T wave) and cutaneous manifestations resulting from a genetic defect in gene encoding plakoglobin which is an essential protein component of intercellular junction[8]. The cardinal symptoms of ND are related to the derangement of adhesive function due to deficiency of plakoglobin[43].

Inherited cardiac conduction defects in dogs

Sudden death syndrome in German shepherd

Sudden death syndrome in German shepherd is caused by an inherited cardiac arrhythmias characterised a sudden death during sleep in the early morning or during rest shortly after exercise[31]. Inheritance mode was reported to be a sex-linked or autosomal dominant trait[32]. It is more vulnerable in young dogs and mostly has no obvious clinical signs, cardiographical abnormalities and even no postmortem findings. Death is mainly due to malignant ventricular tachycardia (VT) progressing to ventricular fibrillation (Fig 4). Electrocardiographic signs are variable from infrequent premature ventricular complexes (PVCs) to numerous PVCs, pairs, triplets, and frequent runs of VT. The VT is most frequently (85%) rapid (rate >300 beats/min), polymorphic and nonsustained. The paroxymal polymorphic VT (85%) is more common than sustained monomorphic VT (15%) in affected dogs. The ventricular arrhythmia is age dependent[33]. PVCs are rare before 12 weeks of age and between the ages of 24 to 28 weeks[33]. After 28 weeks the frequency is gradually declined and no longer existed after 100 weeks of age.

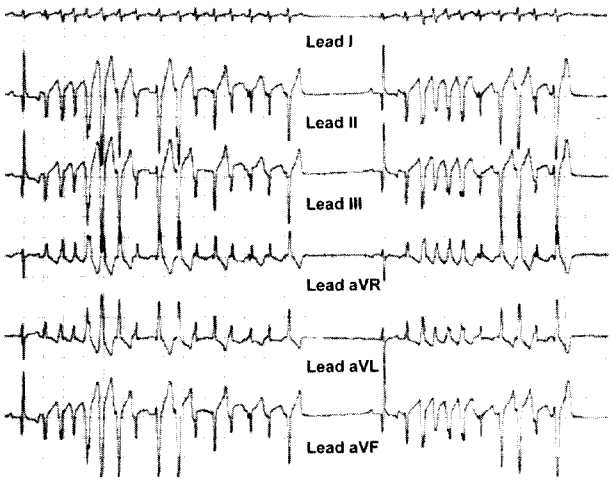

Fig 4. Sudden death syndrome in German shepherd. On ECG, the dog showed nonsustained polymorphic ventricular tachycardia (*Torsade de pointes*) preceded the ventricular fibrillation at 16 weeks of age. The dog died during sleep at 14 months of age. (25 mm/s, 5 mm=1 mV). Permission from Dr Moise NS.

According to current studies, mechanism(s) of the arrhythmia in this dog breed are:

1) perturbations in the autonomic nervous system: the death during sleep and higher frequency of VT during rapid eye movement sleep (REM) suggested that an elevated parasympathetic tone during sleep is triggered sympathetic activity tone so thus ventricular arrhythmias may be induced.
2) lacking and heterogeneous innervation: Purkinje fibers lacked innervation tends to induce triggered activity and the heterogeneous innervation in these cells can disperse refractoriness and can develop reentrant arrhythmia
3) developmental arrest in tissues involved in conduction: Reduced cell capacitance, reduced I_{to} (transient outward potassium current) current density and regional paucity of sympathetic nerve fibers can be evidence for conduction defects possibly originated from the developmental stage of conduction tissues
4) abnormal ventricular repolarization: the triggered activity

and a reduced current I_{to} strongly suggested that there is defective ventricular repolarization in this dog breed.

The abnormal ventricular repolarization due to structural derangements in this dog breed is similar to human the long QT syndrome, Brugada syndrome, catecholaminergic idiopathic ventricular tachycardias, and the short-coupled *torsade de pointes*[10]. Furthermore, perturbations in the autonomic nervous system causing sudden death in this dog can be similarly noticed in sudden infant death syndrome (SIDS) by cardiac cause[48]. Moreover, abnormal sympathetic innervation has been identified in patients with Brugada syndrome which, like these dogs, does not display prolongation of the QT interval[19,62]. and in some patients with the long-QT syndrome[1]. Despite phenotypic variance in each human disease, an abnormal ventricular repolarization and an influence by the autonomic nervous system[9], which are mainly cause of VT and sudden death in German shepherd, are commonly noticed in all diseases.

Sudden death syndrome in Boxer

Sudden death syndrome in Boxer is characterized by ventricular tachyarrhythmias followed by syncope or sometimes sudden death. It is more common in adult dog, 2-8 yrs of age and often associated with exercise and excitement[23,29]. Recent study showed that the inheritance of this syndrome is autosomal dominant[16]. Most affected dogs have no obvious abnormalities in diagnostic cardiology except VT in electrocardiogram (Fig 5).

Ventricular fibrillation is the main cause of death and usually proceeded by a rapid monomorphic VT. Premature ventricular complexes (PVCs) are predominantly observed in most affected dogs and progresses to VT or bradyarrhythmias in some affected dogs.

Clinical signs vary from no obvious signs to ventricular arrhythmias during routine examination. Some dogs have signs of left heart failure associated to myocardial failure but some have a syncope or sudden death without detectable cardiac disease. In addition, in some cases, myocardial failure can be proceeded by syncope due to ventricular arrhythmias. Furthermore, there is no correlation between the severity of the arrhythmia and the presence of coexisting myocardial failure. Histopathological features are variation in myofiber size, loss of myofibers, fibrosis and fatty infiltration and the lesions are more obvious in the right ventricular free wall. The affected dogs respond to type III antiarrhythmic therapy (e.g. sotalol or atenolol).

Some features of sudden death syndrome in Boxer are similar to arrhythmogenic right ventricular dysplasia in human[16,23,26], although there are some discrepancies between these two diseases.

Sick sinus syndrome in Miniature Schnauzers

Sick sinus syndrome of the Miniature Schnauzer is more common in middle-aged female (6 to12 year of age) and is characterized by syncope with prolonged sinus pauses. The

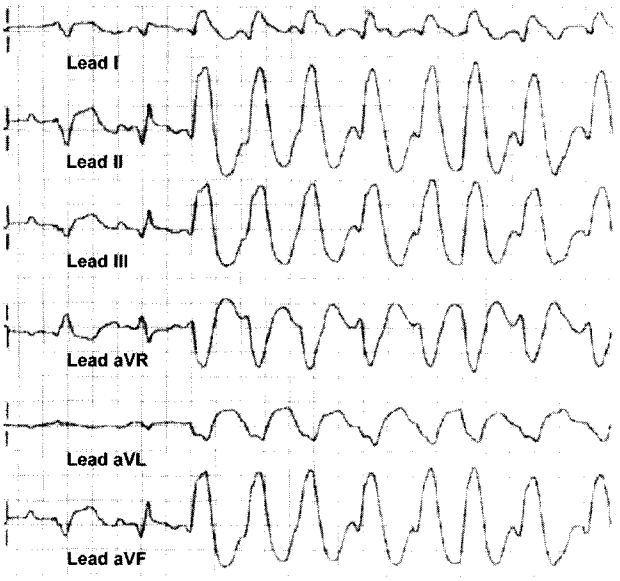

Fig 5. Sudden death syndrome in Boxer. On ECG, the dog showed ventricular tachycardia with a right bundle branch block. The ventricular tachycardia is monomorphic (compare polymorphic ventricular tarchycardia in Fig 4). The dog died suddenly. (50 mm/s, 5 mm=1 mV). Permission from Dr Moise NS.

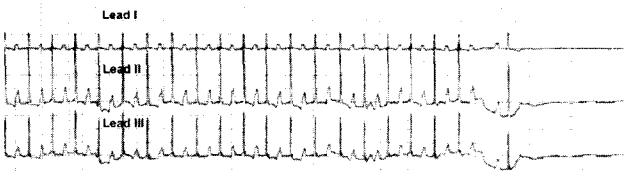

Fig 6. Sick sinus syndrome in Miniature Schnauzer. Supraventricular tachycardia followed by sinus pauses is recorded on ECG in this dog. (25 mm/s, 10 mm=1 mV). Permission from Dr Moise NS.

inability of the junctional tissue to discharge before subsidiary pacemakers in the ventricle and the occurrence of supraventricular tachycardias are the main causes of this syndrome.

In ECG, the affected dogs showed junctional escape complexes progressing to ventricular escape complexes and caused to sinus pauses (Fig 6). However, not all affected dogs have sinus pauses. Inappropriate sinus bradycardia due to escape beat can be occurred in some affected dogs. Mitral valve insufficiency caused by prolapse of the leaflets and fibrous deposition in the valve leaflets is a common gross finding in affected dogs. Although initially a cardiac pacemaker can help preventing syncope, the prognosis is gloomy due to high chance for congestive heart failure by the mitral valve insufficiency in the end.

Although the disease is more common in female, the exact mode of inheritance has not been identified[15]. Similar syndrome has also been found in West Highland White terriers

and Dachshunds dogs and humans.

Atrial standstill in English Springer Spaniels

A familial atrial standstill has been recently reported in the English Springer Spaniel[17]. Despite strong suspicion for inheritance, the exact genetic mechanism has not been identified. It is more common in young adults ranged from 1 to 3 years of age. Clinically, the affected dog usually showed syncope, lethargy or congestive heart failure. Facioscapulohumeral atrophy, which is similar to human inherited facioscapulohumeral muscular dystrophy, has been noticed in some affected dogs.

The clinical features seen in the English Springer Spaniel with atrial standstill are similar to human condition. In ECG, the affected dog has a bradycardia of junctional escape complexes and no identifiable P waves[17]. Typically the affected atria are dilated with thin walls of fibrous connective tissue. In this breed of dog, the atrial standstill can be occurred with other organ disorder such as slowly progressive temporal muscle atrophy, dyserythropoietic anemia and megaesophagus or can be occurred with congestive heart failure with dilation of right and left atrium. Prognosis is bad although a pacemaker implantation can speed down the progress of disease. Other than human inherited facioscapulohumeral muscular dystrophy, some features of atrial standstill in this dog are similar to Emery-Dreifuss dystrophy, permanent atrial paralysis, atrial arrhythmias and abnormalities of atrioventricular conduction in human[17,18,53,56].

Conclusion

A number of human inherited cardiac disorders and their genetic aetiologies and pathogeneses were discussed. Canine conduction defects similar to certain type of human conduction defects were also discussed. Investigation of inherited canine conduction defects will be useful for understanding cardiac arrhythmogenesis and molecular genetic mechanism in dogs and humans.

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개와 사람의 선천성 심장 전도장애에 대한 분자 유전학적 이해

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요 약 : 심장 전도계에 관련된 심장 질환은 심장 전도계의 원발성 결함이나 형태학적 심장 질환 및 약물 중독같은 속발성 원인에 의해 발생한다. 특히 선천성 심장 전도 장애의 경우, 이온 채널, 이온 채널에 관련한 세포질성 단백질, gap-junction 단백질, transcription factors (심장 발생에 관련된 유전자들) 및 kinase subunit을 전사하는 유전자의 돌연변이가 원발성 선천성 심장 전도장애의 원인으로 밝혀지고 있다. 사람의 부정맥 발생에 관련된 발병기전에 커다란 진보가 이루어지고 있음에도 불구하고, 개의 경우, 저먼 세퍼드의 급사 증후군 (sudden death syndrome)을 제외한 다른 전도 장애에 대한 연구는 극히 미비한 상태이다. 본 종설에서는 지금까지 밝혀진 심장 부정맥 발생의 분자 유전학적 고찰과 이와 관련된 사람의 유전학적 질환들과 이와 유사한 개의 선천성 심장 전도 장애에 대해 연구 고찰하였다.

주요어 : Long-QT 증후군, 급사, 선천성 심장전도장애, 이온채널, 심부정맥