STRESS AND LONG QT SYNDROME: THE ROLE OF STRESS PRONENESS AND ENVIRONMENTAL STRESS

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Stress and long QT syndrome: 
the role of stress proneness and 
environmental stress

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ABSTRACT

Sudden deaths among seemingly healthy young individuals often have a cardiac origin. The long QT-syndrome (LQTS) is one of such potentially lethal cardiac conditions. LQTS is inherited and congenital, and it is typically characterized by a prolonged QT-interval in the electrocardiogram. The mutations that cause LQTS are known and they form several different LQTS subtypes. These mutations most commonly affect the potassium-channel encoding genes KCNQ1 and KCNH2 which define subtypes LQTS1 and LQTS2, and the sodium-effecting ion channel gene SCN5A which defines the subtype LQTS3. It is still unknown why some LQTS mutation carriers become symptomatic while others do not. Previous studies have attempted to uncover the causes behind LQTS symptoms by asking patients about specific events in their imminent environments during symptom onset (“what were you doing/what happened before you had the arrhythmia”). However, these studies typically have not employed rigorous psychometric questionnaires.

In the current studies, data from 70-259 symptomatic and 103-328 asymptomatic LQTS mutation carriers, 203 relatives and 79-2056 people from the general Finnish population were utilised.

The goal of the thesis was to study what causes symptoms in LQTS. More specifically, it was studied whether or not the symptomatic LQTS mutation carriers differ from asymptomatic ones in their stress proneness, as measured by two temperament scales: Cloninger's TCI and Gray's RST. In addition, to assess environmental stress, questionnaires measuring work stress based on the models by Karasek and Siegrist and their job control-demand and effort-reward scales were employed.

Also two additional measures (scales) were employed to assess the interaction between environment and personality traits related to experiencing stress. First, Framingham’s type A scale was employed to assess stressful work involvement – i.e., individual tendency to experience one's working environment as stressful. Second, the Cope questionnaire and Stressful life events scale were employed to measure the level of emotional distress subjects experienced in response to a stressful life event in the past 12 months.
The results indicated that all LQTS mutation carriers (symptomatic and asymptomatic) were equally stress prone, as measured by stress-related temperament sub-scales (harm avoidance and behavioural inhibition). However, the symptomatic patients experienced higher levels of work stress of both scales. In addition, the symptomatic patients experienced higher levels of both stressful work involvement and emotional distress in response to a stressful life event in the past 12 months.

Subsequent research should combine the data on the environmental stressors which most likely lead to symptoms, whereby a putative risk score system could be established. Risk scores would enable identifying individuals who are at high risk. Subsequently, pertinent interventions and medical and other attention could be directed at these individuals.
Joka vuosi useita perusterveitä nuoria aikuisia kuolee äkillisesti Suomessa. Useimmiten syyt äkillisille kuolemille ovat sydänperäisiä. Pitkä QT -oireyhtymä (LQTS) on sydämen rytmihäiriösairaus, joka voi johtaa perusterveiden nuorten äkillisiin kuolemiin.

LQTS:n aiheuttavan mutaatiot on selvitetty. Yleisimmät näistä ovat kaliumionikanavamutaatio KCNQ1:ssä tai KCNH2:ssa, jotka aiheuttavat alatyypit LQTS1 ja LQTS2, ja mutaatio natriumionikanavageenissä SCN5a joka aiheuttaa alatyypin LQTS3. LQTS:ää luonnehtii tyypillisesti pidentynyt QT-aika, joka näkyy sydänsähkökäyrässä.


Tässä tutkimuksessa käytettiin 70–259 oireisen ja 103–328 oireettoman LQTS mutaationkantajan, 203 heidän sukulaisensa, ja 79–2056 Suomen yleisväestöön kuuluvan tietoja.


ACKNOWLEDGEMENTS

First and foremost I would like to thank my supervisor and Professor Liisa Keltikangas-Järvinen for giving me the opportunity to work in her great research group. It is an honor to be working under one of the most famous researchers in Finland. You are not only a great researcher but had a wide general knowledge of the world.

Second I would like to thank my supervisor Docent Taina Hintsa for giving important support and supervision during these years. You have even taken personal vacation in order to keep me working for you when the funding has been scarce.

I would like to thank the seniors in my research group: Assistant Professor Markus Jokela for not only being my coauthor and funder but also inspirational figure as well as a great example how someone who is so kind can succeed in the university and research world by being simply talented. I am also very grateful to Docent Laura Pulkki-Råback and Docent Mirka Hintsanen: you have granted very important contribution to my work as coauthors and you have funded my work which I greatly appreciate. Doing the thesis would have literally been impossible without every senior’s contribution. You are the backbone of the group and an important reason why it is so successful.

I would like to thank also all of my colleagues, including Dr. Jussi Palomäki, Pentti Henttonen, Dr. Tom Rosenström, Dr. Marius Lahti, Dr. Christian Hakulinen and others for valuable help and sometimes beer company which may be a combination of making science, stress-reduction and therapy. I would like to thank other members of our research group, including Dr. Päivi Merjonen and Dr. Saija Alatupa, who have been my coauthors and the latter has also shared a room with me. I would like to thank Dr. Sari Mullola and my roommates Kaisa Kaseva and Maria Törnroos for interesting discussions.

Sufficient data sets have been necessary for my work. I would like to thank Docent Heikki Swan for coauthorship, LQTS data and funding. I would like to thank two other coauthors, Professor Kimmo Kontula and Docent Lauri Toivonen for the LQTS data and their coauthorship. In addition I would like to thank Professor Olli Raitakari for the YFS data and coauthorship.

In addition I would like to thank the reviewers Professor Marko Elovainio and Docent Sampsa Puttonen for important and useful comments.

I would like to thank my relatives, colleagues, formers colleagues and former supervisors, especially Dr. Sarah Zala with whom I started my scientific career, and former teachers, especially Dr. Otto Lappi from the university, and primary school teacher Juha Kaplas, who awarded me with a stipend because I always disagreed. I would also like to thank student friends, girlfriends, friends from my early life and other
people who have made me the person I am today. I feel like I am constantly bombarded by great people who direct me into being a better person and a better researcher. I would like to thank also all of the people who deserve credit but were not mentioned.

I would like to thank National Doctoral Programme of Psychology for granting me a position and a long funding.

I would like to thank my mother Satu and father Erkki for making me the person I am. I would also like to thank my grandmother Salme who was always very excited about my PhD thesis and she would always offer me a cup of coffee when I was stressed. She would have been very pleased to see the completion of the thesis.
LIST OF ORIGINAL PUBLICATIONS


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### ABBREVIATIONS

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<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
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<td>BIS</td>
<td>Behavioural inhibition system</td>
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<td>HA</td>
<td>Harm avoidance</td>
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<td>HPA</td>
<td>Hypothalamic–pituitary–adrenal (axis)</td>
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<td>LQTS</td>
<td>Long QT syndrome</td>
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<td>RST</td>
<td>Reinforcement Sensitivity Theory</td>
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<td>SLE</td>
<td>Stressful life event</td>
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<td>TCI</td>
<td>Temperament and character inventory</td>
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<td>YFS</td>
<td>Young Finns Study (general population)</td>
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1 INTRODUCTION

1.1 Long QT syndrome

Sudden deaths among young adults often originate from cardiac problems. In the 1950s, research found that cardiac deaths are not always related to coronary heart disease; often the patients had no typical coronary heart problems. In 1957, researchers described an arrhythmic disorder with a prolonged QT interval visible in the electrocardiograph that was linked to congenital deafness and sudden death (Jervell & Lange-Nielsen, 1957).

The initial theories about the reasons for long QT syndrome were focused on adrenergic stimulus, which proved to be related to symptoms. Researchers attributed the symptoms to abnormalities in the sympathetic nervous system (Schwartz & Locati, 1985). In 1994 and shortly thereafter, researchers found that three genes affecting heart’s ion channels were related to LQTS (Curran et al., 1995; Wang et al., 1996a; Wang et al., 1996b).

Predisposing mutations and thus subtypes of LQTS are numerous, but the most common are LQT1 and LQT2, which are characterized by the occurrence of mutations in the potassium channel genes KCNQ1 and KCNH2. A somewhat rarer subtype is LQT3, which results from mutations in the sodium channel gene SCN5A (Splawski et al., 2000). Only some of the LQTS mutation carriers will exhibit arrhythmic events (e.g. symptoms). The reasons for the symptoms remain partly unknown, but research is still ongoing.

1.2 Risk factors for cardiac symptoms in LQTS

The symptoms of long QT syndrome typically occur during vigorous physical exercise or emotional stress. The first assessments of the mortality rate were very high because identification focused on the most severely affected patients. Beta blocker treatment greatly reduced the mortality rate among long QT patients (Schwartz & Locati, 1985).

As noted, the treatment and understanding of long QT syndrome developed considerably after the discovery that its predisposing mutations affect the ion channels in the heart. However, not all mutation carriers become symptomatic (in this sample,
less than 50% have exhibited symptoms); thus, the phenomenon requires further explanation.

Depending on the mutation subtype, possible proximal reasons for arrhythmic events include physical exercise or swimming, acoustical startling and rest or sleep (Schwartz et al., 2001). LQTS3 subtype is characterised by arrhythmic risk during a slow heart rate (parasympathetic activity), whereas LQTS1 and LQTS2 are characterised by arrhythmias during a rapid heart rate (sympathetic activity). This characterisation is also reflected in the activities most are typically engaged in when their symptoms occur. Arrhythmias in LQTS1 typically occur during exercise, whereas in LQTS3, symptoms typically occur during rest or sleep. However, the explanatory power of such reasons may be insufficient: the measurement itself is not very scientifically rigorous and in addition people cannot avoid many of the activities associated with symptoms (i.e. “rest or sleep” in LQTS3). Thus, when considering the environmental stress linked to the symptoms, “sleeping” is a description rather than an explanation of symptoms.

Documented risk factors include the mutation subtype, as some mutations are more likely to lead to arrhythmic events. Young age (teenage years to early twenties) in males is also a risk factor: as males age, their likelihood of experiencing symptoms decreases. In females, most symptoms occur after 20 years of age. In particular, male children with LQTS1 and adult women with LQTS2 are at higher risk (Liu et al., 2011).

Some of the activities during which the arrhythmias occur are avoidable (swimming), but some not (rest or sleep) (Splawski et al., 2000). Much of the previous research on the psychological stress or well-being on the LQTS symptoms has provided only suggestive and anecdotal evidence (Lane et al., 2009; Scarano et al., 2014; Watson, 2011). Rigorous psychological measurements of the reasons leading to symptoms have been only few and taken place only relatively recently (Hintsa et al., 2009; Hintsa et al., 2010a; Paavonen et al., 2001). It would be vitally important to study whether some or all LQTS patients possess psychological or other stress-related traits that affect their interaction with the environment and whether the stressful environment itself increases affects the increased risk for symptoms in LQTS.
1.3 The concept of stress

In biology, stress can be defined by its purpose: to avoid or escape from a stressor, which is maladaptive for the organism. The stressor may be something that would cause organism imbalance, thus threatening its homeostasis. In more complex organisms, this biological definition is insufficient. Physiologically, stress may mean changes in the nervous, endocrinological and immune systems, changes which may enhance performance. But such stress often becomes too strong, and is then experienced as anxiety or other unpleasant or unhealthy states (Selye, 1976; Cacioppo et al., 2007).

In behavioural medicine, research is often focused on the aspects of stress that influence health either through changes in the nervous and endocrinological systems or in immune system function. For instance, increased levels of cortisol or adrenaline or activation of the sympathetic nervous system over the parasympathetic nervous system could disrupt cardiac function. The possible causal relationship of arrhythmic risk and stress could be connected to sudden and strong sympathetic nervous system activity which increases heart rate. On the other hand, the relationship between cardiovascular disease and stress or depression may involve elevated levels of cortisol. Stress may affect cardiac function in ways that may disturb the normal functioning of the heart (Berntson et al., 2007; Uchino et al., 2007).

1.3.1 Hypothalamic-pituitary-adrenal axis

Much of the research about the complex relationship between psychological and physiological stress has focused on the hypothalamic-pituitary-adrenal (HPA) axis (Selye, 1956, 1976; Chrousos & Gold, 1992). When faced with stress, the hypothalamus secretes corticotrophin-releasing hormone (CRH), which in turn stimulates the anterior pituitary. The anterior pituitary then releases adrenocorticotropic hormone (ACTH) into the main circulatory system, which stimulates the adrenal cortex in the kidneys to produce cortisol. Cortisol inhibits the secretion of CRH and ACTH, thus creating a negative feedback-loop (Cacioppo et al., 2007).

Researchers have suggested that cortisol plays an important role in the adverse effects of stress on health. Elevated levels of cortisol have been linked to both
psychological disorders, such as depression, and physical diseases such as cardiovascular disease. The possible effect of high cortisol levels to arrhythmic risk on LQTS is yet to be explored and therefore remains unknown. In other contexts, elevated levels of cortisol have been associated with increased risk for sudden cardiac death (Drechsler et al., 2013).

1.3.2 Autonomic nervous system

The autonomic nervous system (ANS) is divided into the sympathetic and parasympathetic nervous systems. The sympathetic nervous system becomes excited during stress, whereas parasympathetic nervous system activity decreases (Berntson et al., 2007).

The autonomic nervous system widely innervates different organs in the body, but what makes sympathetic and parasympathetic nervous system function relevant to LQTS research is that they both control the cardiovascular system. The sympathetic and parasympathetic nerves typically exert opposing actions in the target organ (Cacioppo et al., 2007). The sympathetic activation typically raises heart rate and parasympathetic activation lowers it. The major parasympathetic nerve innervating the heart from the brain is called the vagus nerve (Katona & Jih, 1975).

Some computation also takes place in the heart. Parasympathetic ganglia have been called the “heart brain”, referring to the anatomically and neurochemically distinct sets of interacting neurons fact they form that serve to regulate aspects of cardiac function (Randall et al., 1996). Thus, the heart is an independent organ which interacts with the brain and the rest of the body, and its direction of interaction can sometimes be bidirectional.

Both the sympathetic and parasympathetic nervous systems use acetylcholine as a neurotransmitter from the preganglionic neuron to the postganglionic neuron. The postganglionic sympathetic neuron innervates the heart through noradrenaline (norepinephrine) and β1 (beta1) adrenergic receptors, which can also be activated by adrenaline (epinephrine). Beta-blocker medication, which is used to reduce risk for arrhythmias in LQTS, inhibits the functioning of the β-receptors and reduces the effect of sympathetic nervous system activity which typically increases heart rate (thus, beta-
blocker medication is effective only in certain subtypes of LQTS). Postganglionic parasympathetic neurons use acetylcholine to activate muscarinic receptors, which in turn reduce heart rate (Berntson et al., 2007).

Sympathetic and parasympathetic nervous system activation has several health effects, namely stress-induced cardiac events involve the effect of sympathetic activation and parasympathetic withdrawal (Morree et al., 2010; Licht et al., 2013).

1.3.3 Psychological stress

Psychological stress is, in fact, inseparable from stress in general: stress hormones always affect cognition and vice versa, so no clear separation of the biological background and psychological states and cognition is possible. However, discussing psychological stress separately may prove useful because much of the literature in the research field is focused on psychological stress.

The literature provides several definitions of psychological stress which refer to bodily adaptation processes and the maintenance of body’s balance (Selye, 1973; McEwen, 1998). Psychological stress can be defined as a “discrepancy between the environmental demand (real or perceived) and individual capacity (real or perceived), and the meaning of this discrepancy is related to one’s health” (Lazarus & Folkman, 1984). The process model of psychological stress claims that the primary appraisal denotes the evaluation of a challenging situation and estimates if it involves some kind of threat. The evaluation of available resources and abilities to cope with the situation is called the secondary appraisal (Lazarus & Folkman, 1984). Prolonged physiological or psychological stress may harm one’s health. Psychological stress can affect individuals on many levels. First, the physiological level causes changes in the functions of the autonomic nervous system, increasing the secretion of stress hormones, and suppressing the immune system. Second, the health-behaviour level may include increased alcohol consumption, as well as smoking, and physical inactivity. Third, at the level of psychological wellbeing, stress can increase anxiety, depression, and distress (Chandola et al., 2008; Siegrist & Rodel, 2006).
1.3.4 Stress and health in cardiac disorders

Studies have found an association between stress and several disease-types, including cardiovascular disease, infectious diseases and cancer (Cacioppo et al., 2007; Uchino et al., 2007). In cardiovascular disease, stress is associated with both acute and chronic stress as well as with morbidity and mortality. The association between cardiovascular disease and stress differs considerably from the association between stress and an arrhythmic disorder. Stress affects one’s immune response and the process of atherosclerosis via several proposed mechanisms, including cytokines, which affect inflammation, although the ‘reactivity hypothesis’ involving increased heart rate may explain part of the elevated risk observed in stressed patients.

Interestingly, reducing stress may effectively decrease cardiovascular mortality (Uchino et al., 2007). Although we know less about the association between stress and arrhythmic disorders, the causal pathway could likely be somewhat similar to that of other cardiovascular diseases, with the exception of the inflammation processes related to the formation of atherosclerosis (i.e. the possible activation of the sympathetic and the withdrawal of the parasympathetic nervous system as well as high levels of stress hormones such as cortisol). Some or all of these effects, among others, may lead to higher heart rate and blood pressure.

1.4 Temperament and individual differences in stress proneness

Individuals exposed to seemingly similar stresses in the environment, differ in their reactions to them. Some people are more stress prone, whereas others are more resilient to stress. Are there any ways to measure these differences in stress proneness? Some temperament traits by themselves may be markers of stress proneness (Talge et al., 2008): i.e. they are thought to increase one’s likelihood to have high stress reactivity. Thus, one possible approach is to use temperament or personality scales to measure individual stress proneness.
Temperament consists of heritable (Heath et al., 1994), biologically rooted individual differences in behavioural tendencies that emerge early in life and remain relatively stable across various situations and over time (Bates, 1989).

One can measure stress proneness at least with two temperament scales: with Cloninger’s Temperament and Character Inventory (TCI) (Cloninger et al., 1993) and a scale based on Gray’s reinforcement sensitivity theory (RST) (Gray, 1972, 1991). The most relevant measures of stress proneness in the temperament scales are harm avoidance (HA) in Cloninger’s TCI and the behavioural inhibition system (BIS) in the Gray's original RST.

1.5 Cloninger’s psychobiological model of temperament

Cloninger's psychobiological theory of temperament is one of the most widely used concepts in behavioural stress research because it connects temperament with a biological reference and provides a background for a mechanism through which a subjective experience is likely to manifest as physiological symptoms (Cloninger, 1987; Cloninger et al., 1993). Cloninger published the first version of his temperament theory, the “Tridimensional Personality Questionnaire” (TPQ) in 1987 (Cloninger, 1987) and later revised it to the “Temperament and Character Inventory” (TCI) (Cloninger et al., 1993).

The three temperament traits that represent behavioral biases and have their bases in monoamine neurotransmitters are novelty seeking (NS), which is related to the dopamine system and behavioral activation; harm avoidance (HA), which is related to the serotonin system and behavioral inhibition; and reward dependence (RD), which is related to the noradrenalin system and maintenance of social rewards (Cloninger, 1987; Cloninger et al., 1993).

1.5.1 Harm avoidance

HA is a temperament trait included in Cloninger’s psychobiological model of temperament (Cloninger et al., 1993). It refers to a heritable tendency to react to stress-evoking stimuli with emotional distress and behavioural avoidance (Cloninger, 1987).
and has been associated with higher levels of fear as well as unpleasant emotions and lower levels of positive emotions various stressful tasks (Puttonen et al., 2005). In addition, when measured by heart rate and heart rate variability, HA associated with low parasympathetic control (Puttonen et al., 2008). Low parasympathetic control of the heart rate, in turn, is related to cardiac events (myocardial infarction, angina pectoris, death from coronary heart disease, or congestive heart failure) (Tsuji et al., 1996). The cortisol awakening response was lower in subjects with low harm avoidance, which suggests that HA is a marker for stress proneness (Rademaker et al., 2009).

1.6 Gray’s reinforcement sensitivity theory of temperament

Jeffrey Alan Gray developed the first version of the reinforcement sensitivity theory of personality (RST) in the early 1970s based on the combination of the data collected from animal studies with our accumulating knowledge of the function of neurotransmitter systems in the mammalian brain, in addition to influences from the descriptive personality model of Eysenck (Corr, 2004). Gray’s theory assumed that different neurotransmitter systems are related to different aspects of animal and human behaviour. The RST theory originally incorporated three systems: the behavioural activation system (BAS), the behavior inhibition system (BIS) and the flight and fight system (FFS). BAS handles with conditioned and unconditioned reward systems of the brain. BIS processes conditioned aversive stimuli and is often called the punishment system. FFS is connected with aversive unconditioned aversive stimuli. High BAS activity in a person may lead to impulsivity, and high BIS activity may lead to sadness, fear and anxiety, whereas FFS may lead to rage and panic (Gray, 1991).

The modified new theory also incorporates three systems, but they serve slightly different functions: the modified BAS is related to all appetitive behaviours, and the modified FFFS (one additional “F” for freezing) concerns all negative responses, whether conditioned or unconditioned. The modified BIS concerns the decision system that evaluates contradictory information between the two systems (BAS and FFFS) and conflicting information between the two systems causes anxiety (McNaughton & Gray, 2000; Corr, 2004).
The revised theory may lead to confusion, so it is important to note that the theory on which Gray’s temperament questionnaire is based is the original one. The questionnaire only includes BAS and BIS, and of these, BIS is more relevant to this study, as it reflects stress proneness, whereas the meaning of the BAS would be difficult to understand.

1.6.1 Behavioural inhibition

Behavioural inhibition (BIS) is a stress-related temperament trait that is linked to the function of the neurotransmitter serotonin. When faced with aversive stimuli, a tendency towards high BIS activity is likely to heighten one’s arousal, attention and emotional distress, which lead to an increase in behavioural inhibition (Gray, 1991). Evidence suggests that BIS sensitivity magnifies reactions to stressful life events (Gable et al., 2000), which, in turn, are linked to arrhythmic risk in LQTS (Hintsa et al., 2010a). Furthermore, studies have linked BIS with physiological stress reactivity in terms of electrical skin conductance (Arnett & Newman, 2000), proneness to higher negative emotions during challenges (Heponiemi et al., 2003) and stress-related cardiac reactivity (i.e. higher heart rate and parasympathetic withdrawal) (Keltikangas-Järvinen et al., 1999).

1.7 Stressful work involvement

Stressful work involvement refers here to a cognitive style in which the individual continues to ponder about work after working hours and experiences work as a stressful environment, which stretches the individual to the limit. Stressful work involvement is not an established concept in a similar way as work stress is and it does not differentiate between the individual’s experience of the work place and objective reality of the work place itself. Thus, separating between the individual traits from the features of the workplace is harder as the concept does not take into account the individual’s occupational status or other factors involving the stressfulness of the work place. Even so, compressing into a few questions whether the individual experiences stress in the work context, can prove useful, whatever the underlying reason for the reported stress.
Stressful work involvement can be estimated from questions derived from the Framingham type A scale (FTAS) (Haynes et al., 1980).

### 1.8 Work stress

Two scientifically widely tested work stress models include Karasek’s (1979) job demands-job control model (or job strain model) and Siegrist’s (1996) effort-reward imbalance model (Karasek, 1979; Karasek & Theorell, 1990; Siegrist, 1996; Siegrist et al., 2004).

#### 1.8.1 Karasek’s model of work stress

In Karasek’s model, job demands refer to time pressures and an excessive work load, and job control refers to employees’ opportunities to use social, organisational and personal resources in their work tasks and environments (Karasek, 1979; Karasek & Theorell, 1990). Job strain is assumed to result when job demands are high and job control is low (Karasek, 1979). Thus, people can cope with even a highly demanding job if their job control is high.

#### 1.8.2 Siegrist’s model of work stress

Siegrist’s effort-reward imbalance model is based on social exchange theory, and emphasises current social exchange processes in a work context (Siegrist, 1996; Siegrist et al., 2004). Efforts refer to demands and obligations of work, such as time pressures and task difficulty. Rewards denote esteem rewards, monetary rewards, job security and career development opportunities. If effort is not rewarded, an effort-reward imbalance condition may occur, resulting in a condition of high efforts and low rewards, which is assumed to induce work stress in the majority of employees (Siegrist, 1996; Siegrist et al., 2004).

Studies have shown that higher job strain and effort-reward imbalance are related to increased risk for cardiovascular disease (Siegrist, 1996; van der Doef & Maes, 1999; Belkic et al., 2004; Hintsa et al., 2010b; Hintsanen et al., 2005; Kivimäki et al., 2002;
van Vegchel et al., 2005a), and that higher effort-reward imbalance at work or lower reward increase the risk for recurrent cardiac events (Aboa-Eboule et al., 2011). Work stress may also increase the risk of arrhythmia in LQTS through altered autonomic function, as studies show that autonomic tone and reflexes are related to increased risk for arrhythmias (La Rovere et al., 2001; Schwartz et al., 2008; Schwartz et al., 1988). Studies have demonstrated markers of reduced parasympathetic nervous system (i.e. vagal) activity, such as suppressed baroreflex sensitivity and heart rate variability, to be predictors of cardiac mortality (La Rovere et al., 2001). Some evidence suggests that stress-inducing work characteristics may burden the vascular and nervous system (Collins et al., 2005; van der Palen et al., 1995; Douglas et al., 1995; Schwartz & La Rovere, 1998).

1.9 Emotional distress and environmental stress

An essential marker of high stress-proneness is high emotional distress when confronting environmental stress (Melamed, 1996). When confronting stressful life events (SLEs), such as divorce, unemployment or death of a close person, a person usually experiences very strong emotional and physiological arousal (Rahe, 2000). The literature provides evidence that the intensity of the arousal differs between people (Lazarus & Folkman, 1984), and the amount of negative affectivity after experiencing stress is relevant, as it may prove more maladaptive than experiencing positive affect (Folkman & Moskowitz, 2000). One can measure emotional distress with the Cope questionnaire (Carver et al., 1989), and SLEs with the Social Readjustment Rating Scale (Holmes & Rahe, 1967).

1.10 Overview of stress measurement and LQTS

Several different levels of the stress “chain” were measured in the current thesis (Figure 1). Environmental stress is experienced and processed by the individual and finally it may lead to adverse and even pathological states. Directly accessing people’s stress or stressful experiences (top row) is impossible, but several different indirect stress measurements (middle row) can be used and then combined with the knowledge about
the LQTS symptom status. This way it is possible to have a complete picture about what aspects in the environment cause symptoms.

Environmental stress can be measured by several means, including questionnaires developed for measuring work stress and stressful life events. In many ways, there is no “objective” stress in the environment, but the negative effects of an event or environmental condition are always dependent on the interpreter or the person. The way in which environmental stress affects health outcomes is always dependent on the individual stress perception and processing, which may include temperamental stress proneness and other response styles to environmental stress. The reason why harm avoidance, behavioural inhibition and response style after a stressful life event were measured, was that individual difference may affect stress perceptions that may be associated with symptoms. Also stressful work involvement may reflect individual response styles of stress in work: it is considered as a phenomenon originating from the combination of personal stress proneness and the work environment context.

As can be noted from Figure 1, it there is no simple way of categorising different aspects of stress: some of the measured variables could affect several different aspects of stress chain and its measurement. For instance, stress prone temperament most likely affects the coping styles of an individual. In addition, it is not clear how well people who have had a burdening life event separate between their current state of anxiety and their general stress-processing: thus the same variable “emotional distress” could be categorised other ways as well. Also, it should be noted that other pathways and interactions exist as well and this model is extremely simplistic: for instance, personality affects how individuals choose their stress-environment.

There are other measures which were not included in the study but that have been studied previously in the same sample: depression, vital exhaustion and number of stressful life events (Hintsa et al., 2009; Hintsa et al., 2010a). Also, the research is ongoing in the psychophysiology and affects of LQTS mutation carriers during stress.
Figure 1. The stress chain: from stressful environment to pathological stress states (horizontal arrows) and the ways in which different levels of stress can be measured and connected with symptoms in LQTS (vertical arrows). Measured variables are bolded.
2 AIMS OF THE STUDY

The aim of the study was to understand what causes symptoms in LQTS. The options include innate the stress proneness of symptomatic LQTS mutation carriers and the stressful environmental conditions that symptomatic LQTS mutation carriers experience, or a combination of both.

The study questions are based on two main themes: a) whether symptomatic and asymptomatic LQTS mutation carriers possess innate or environmental differences and b) whether LQTS mutation carriers have some innate psychological differences from other people, especially the healthy general population.

2.1 Study Questions

2.1.1 Studies I and II

Do symptomatic LQTS mutation carriers have more stress-prone temperament (HA and BIS) than asymptomatic LQTS mutation carriers?
Are LQTS mutation carriers more stress-prone than non-carriers of the general population in terms of their temperament (HA and BIS)?

2.1.2 Study III

Do symptomatic LQTS mutation carriers have higher stressful work involvement than asymptomatic LQTS mutation carriers?
Do LQTS mutation carriers have higher stressful work involvement than the general population?

2.1.3 Study IV

Does higher work stress measured by either job strain or effort-reward imbalance associate with a higher likelihood of arrhythmias in LQTS mutation carriers?
Do LQTS mutation carriers differ from the healthy comparison groups in their work stress measured either by job strain or effort-reward imbalance.

2.1.4 Study V

Do the symptomatic LQTS mutation carriers have higher the emotional distress after a stressful life event than asymptomatic LQTS mutation carriers?
3 METHODS

3.1 Participants

The participants were recruited from two study populations: the Finnish LQTS registry and the Young Finns Study (YFS). The number of participants varied depending on the variable and the study.

Table 1. Number of participants in studies

<table>
<thead>
<tr>
<th>Temperament traits</th>
<th>Symptomatic LQTS mutation carriers</th>
<th>Asymptomatic LQTS mutation carriers</th>
<th>Young Finns Study population</th>
<th>LQTS relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harm avoidance (Study I)</td>
<td>259</td>
<td>328</td>
<td>2056</td>
<td></td>
</tr>
<tr>
<td>Behavioural inhibition (Study II)</td>
<td>256</td>
<td>327</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Stressful work involvement (Study III)</td>
<td>164</td>
<td>229</td>
<td>1368</td>
<td></td>
</tr>
<tr>
<td>Work stress (Study IV)</td>
<td>70</td>
<td>103</td>
<td>1209</td>
<td>203</td>
</tr>
<tr>
<td>Emotional distress (Study V)</td>
<td>209 (82)</td>
<td>274 (85)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.1.1 LQTS mutation carriers

The LQTS mutation carriers recruited from the Finnish LQTS registry, which includes all LQTS mutation carriers who participated in molecular genetic studies at the Helsinki University Central Hospital from all over the country since 1993. At present, the registry comprises 1400 mutation carriers and 1700 unaffected relatives. Registry subjects included those who fulfilled the following criteria: molecularly verified positive or negative mutation carrier status for the LQTS-causing mutation, age from 16 to 65 years, residence in Finland, and written informed consent conforming to the ethics guidelines of the Helsinki University Central Hospital. Other studies have described in detail the mutations in KCNQ1, KCNH2, or SCN5A genes and their consequences have been described in detail (Fodstad et al., 2004; Laitinen et al., 2000; Paavonen et al., 2001; Swan et al., 1998). The mean follow-up time was six years since placement on the registry.

Altogether 425, 145 and 17 carriers of the KCNQ1 (G589D, n = 296; IVS7-2A>G, n = 45; D317N, n = 17; R518X, n = 12; other, n = 55), KCNH2 (L552S, n = 53; R176W, n = 41; del453C, n = 20; G584S, n = 9; other, n = 22) and SCN5A (E1784K, n = 5;
I239V, n = 4; V1667I, n = 8) mutations, respectively, participated in the studies, some of which had fewer participants than this due to missing variables.

3.1.2 General population (YFS)

The Finnish population data consisted of participants from the Young Finns Study (YFS), a prospective follow-up study of cardiovascular risk factors in the Finnish population. The design of the study and the selection procedures have previously been described in detail (Åkerblom et al., 1991; Raitakari et al., 2008). There were no diagnosed or suspected LQTS mutation carriers in this data based on the medical examination of each participant in 2001 (Raitakari, personal communication, 31 Aug, 2009). The number of participants varied between different studies (see Table 1).

3.1.3 Description of the separate studies

3.1.3.1 Study I

The study subjects included 587 LQTS mutation carriers from the Finnish LQTS registry and 2056 individuals from the YFS, a database study, representing the general population and serving as control subjects. The LQTS subjects were divided into symptomatic (n = 259) and asymptomatic (n = 328) groups, according to their history of arrhythmic events.

Temperament was assessed using Cloninger's Temperament and Character Inventory (TCI) (Cloninger et al., 1993), which measured novelty seeking, harm avoidance and reward dependence. Subjects missing temperament or background data were excluded. Those excluded did not significantly differ in terms of sex and age from the included participants.

Temperament and background data were available for 2056 persons from the entire sample of 3596 persons from the general Finnish population. The YFS participants included in this study were slightly older (mean age 37.6 vs. 37.3, p < 0.05) and more often female (58.9% vs. 40.3%, p < 0.001) than those due to missing data.
The participants provided their written consent and the ethics committees of the participating universities approved the study.

3.1.3.2 Study II

The study subjects included 583 LQTS mutation carriers (256 symptomatic and 327 asymptomatic) from the Finnish LQTS registry and 79 healthy subjects randomly derived from the population-based sample (YFS). Temperament was assessed Carver and White’s BIS/BAS scale (Carver & White, 1994).

The LQTS mutation carriers with missing background or temperament data were excluded (n = 13).

The participants from the general population were a randomized sample of those who participated in the fifth follow-up of the YFS study and were living in the urban and rural districts of Helsinki (n = 343). They were invited to the experiment until the desired number (n = 96) agreed to participate. Details of this sample are given by Heponiemi and colleagues (2003). In the present study, 79 subjects had complete psychological data, and 17 subjects were excluded due to missing data. There were no age differences between the included and excluded participants.

3.1.3.3 Study III

The study subjects included 164 symptomatic and 229 asymptomatic LQTS mutation carriers from the Finnish LQTS registry and 1368 comparison subjects randomly derived from the population-based sample (YFS). Stressful work involvement was measured with questions derived from the Framingham type A scale (FTAS) (Haynes et al., 1980).

There were 164 symptomatic and 229 asymptomatic LQTS mutation carriers included in the study. Exclusion criteria were the following: missing information on sex, age, stressful work involvement and current employment or not being currently employed. Among symptomatic LQTS mutation carriers there were 97 excluded (76 not currently employed and 13 missing information on work status). Among the asymptomatic LQTS mutation carriers there were 106 excluded subjects (88 not
currently working and 12 missing information on employment status). Excluded symptomatic LQTS mutation carriers scored lower in work involvement (1.33 vs. 1.54; \( p < 0.001 \)), and did not significantly differ in sex (percent female: 80.4\% vs. 69.5 \%, \( p = 0.054 \)) and age (44.08 vs. 41.69, \( p = 0.166 \)) from the included ones. Excluded asymptomatic LQTS mutation carriers did not differ from the included in stressful work involvement (1.46 vs. 1.40, \( p = 0.191 \)), and in addition did not differ in sex (percent female: 60.4 \% vs. 55.0 \%, \( p = 0.358 \)) or age (40.0 vs. 40.1, \( p = 0.537 \)) from the included ones.

There were 1368 YFS participants in the study. The exclusion criteria were the same as in LQTS mutation carriers, i.e. the subjects who had missing information on any of the study variables were excluded. In addition subjects who were not currently employed were 34 excluded. Among the general population, there were 2284 excluded (264 not currently employed and 1589 missing information on their current employment status). Excluded subjects did not differ from the included ones in stressful work involvement (1.41 vs. 1.39, \( p = 0.173 \)), but they were more often males (53.3\% vs. 42.2 \% \( p < 0.001 \)) and younger than the included ones (31.2 vs. 31.8, \( p = 0.001 \)).

3.1.3.4 Study IV

The sample comprised of 70 symptomatic and 103 asymptomatic LQTS mutation carriers and control groups of 203 relatives without the family mutation, and of 1209 population-based YFS control subjects. Work stress was assessed with Karasek’s Job Content Questionnaire (Karasek, 1985) and effort and reward were measured with three-item scales from the Occupational Stress Questionnaire (Elo et al., 1990; Hintsa et al., 2006).

LQTS patients were recruited from the Finnish LQTS registry, which had available 419 persons working full time in 2006. Of these, 394 reported their education and occupation, which the present study required. Because information on some of the other study variables was missing, the final material comprised of 376 participants, including 70 symptomatic and 103 asymptomatic LQTS mutation carriers, as well as 203 control subjects consisting of relatives of LQTS patients with no LQTS-causing mutation. In
addition, the analyses comparing symptomatic and asymptomatic LQTS mutation carriers and their unaffected relatives were, controlled for the use of beta blockers.

In addition, 1209 individuals recruited from the general Finnish population (YFS) subjects (Åkerblom et al., 1991; Raitakari et al., 2008), with complete data for all study variables, served as controls.

3.1.3.5 Study V

The participants numbered 209 symptomatic and 279 asymptomatic LQTS mutation carriers. Emotional distress was assessed with the Cope questionnaire (Carver et al., 1989) and stressful life events (SLEs) with the Social Readjustment Rating Scale (Holmes & Rahe, 1967). Of the 209 symptomatic LQTS mutation carriers, 82 (39.2%) had faced an intermediately to extremely stressful life event in the previous 12 months. Of the 274 asymptomatic LQTS mutation carriers, 85 (31.0%) had recently faced an intermediately or extremely stressful life event.

52 symptomatic and 61 asymptomatic LQTS mutation carriers were excluded due to missing information on relevant study variables (i.e. no reported symptom status, age, emotional distress or occurrence of SLEs). Those excluded showed no differences from the included participants (all p-values > 0.05) in terms of sex, symptoms status or the occurrence of recent burdening SLEs. Those excluded were on average older than those included in the study (46.15 vs. 40.65 years, p = 0.002).

3.2 Measures

3.2.1 Arrhythmic events

Arrhythmic events (i.e. symptoms) were registered when a self-reported questionnaire indicated the subject is inclusion in the database. Sudden loss of consciousness for any arrhythmic reason was counted as an arrhythmia, as well as a documented LQTS-type ventricular arrhythmia and cardiac arrest. A typical vasovagal fainting did not qualify as an arrhythmia. Those who had arrhythmias were categorised as symptomatic. In 2006, H. Swan estimated the arrhythmic status for all of the studies.
3.2.2 Temperament

3.2.2.1 Cloninger's TCI (Study I)

Harm avoidance was assessed in 2006 among LQTS mutation carriers and in 2007 among the YFS subjects with the Temperament and Character Inventory (TCI) (Cloninger et al., 1993). The data were collected by sending the questionnaire to each the subject’s home address. All the subjects received the same information in the letter and completed the questionnaires themselves. The Temperament and Character Inventory consists of the following temperament traits: novelty seeking (NS), harm avoidance (HA) and reward dependence (RD). The temperament scale consists of a total of 107 items. The dimensions were self-rated by the subjects on a five-point Likert scale ranging from totally disagree (1) to totally agree (5). Mean scores for the three temperament traits were calculated. The reliabilities (Cronbach's $\alpha$) for NS, HA, and RD were 0.85, 0.93, and 0.82, respectively. This study was concerned with the temperament trait HA.

3.2.2.2 Gray's RST (Study II)

Behavioral inhibition was measured in 2006 for the LQTS mutation carriers (see Hintsa et al., 2009) and in 1999 for the general population (see Heponiemi et al., 2003) with Carver and White’s BIS/BAS scale (Carver & White, 1994). The scale consists of a BIS scale, which reflects the BIS, and a BAS scale, which reflects the BAS (Carver & White, 1994). The questionnaire used in this study is based on the original Reinforcement Sensitivity Theory. The BIS scale consists of seven items, including ‘I worry about making mistakes’ and ‘I have very few fears compared to my friends’ (reverse scored) (Heponiemi et al., 2003). The subjects self-rated the dimensions on a five point scale (5 = describes me very well, 1 = doesn’t describe me at all) as opposed to the more commonly used 4-point scale. The present study used the mean score for the BIS temperament trait. The reliability (Cronbach’s $\alpha$) of the BIS scale was 0.78 among the LQTS mutation carriers and 0.82 in the YFS population.
3.2.3 Stressful work involvement (Study III)

Three items from the Framingham Type A Scale (FTAS) were used to assess stressful work involvement in 2006 among LQTS mutation carriers and in 2001 among YFS subjects (Haynes et al., 1980). Stressful work involvement refers here to stressful loading resulting from worry about and dissatisfaction with one’s work. The questions were as follows: “Feeling at the end of an average day at work: a) work stayed with you, so you were thinking about it after working hours; b) work often stretched you, to the very limits of your energy and capacity; and c) often felt uncertain, uncomfortable, or dissatisfied with how well you were doing at work.” The response options to each question were in yes/no (0 or 1) format to each question and sum of these answers was the total score of stressful work involvement (0-3). The reliability (Cronbach’s α) of the work involvement scale was 0.60 for the LQTS mutation carriers and 0.52 for the YFS population.

3.2.4 Work stress (Study IV)

3.2.4.1 Job strain

Job control was measured with a nine-item scale from Karasek’s Job Content Questionnaire (Karasek, 1985). The responses of job control (Cronbach’s α = 0.88) were given on a five-point Likert scale with 1 = strongly disagree, and 5 = strongly agree. Job demands (α = 0.64) were measured using a three-item scale from the Occupational Stress Questionnaire (Elo et al., 1992), which has been validated in Finland in 25000 employees. The items were “Do you have to hurry to get your work done”, “Does your work have phases that are too difficult?”, and “Is your work mentally straining?”. The responses were given on a scale ranging from 1 = strongly disagree to 5 = strongly agree. The linear job strain indicator was obtained by subtracting the job control score from the job demands score (Landsbergis et al., 1994).
3.2.4.2 Effort-reward imbalance

Because the standard long version of Siegrist’s (Siegrist, 1996; Siegrist et al., 2004) effort-reward imbalance measure was unavailable for this study, a shorter measure which has served in previous Finnish work stress studies was applied (Hintsa et al., 2010b; Hintsa et al., 2007). Effort and reward were measured with three-item scales from the Occupational Stress Questionnaire (Hintsa et al., 2006; Elo et al., 1990) which resemble the items of the original effort-reward imbalance questionnaire. The number of items in the proxy measure was lower than that in the original measure (effort: 3 versus 6; reward: 3 versus 11). Effort (Cronbach’s $\alpha = 0.64$) was measured with the same three items from the OSQ as with job demands. Reward ($\alpha = 0.61$) was measured with the following three items: “Do you get help and support from your superior if needed?” “How do your coworkers get along with each other in the work place?” and “How satisfied are you with your current employment?” Responses to the effort and reward items were given on a five-point Likert scale; the higher the value, the greater the effort and reward. A mean value was calculated. Effort-reward imbalance was formed by dividing efforts by rewards. Values exceeding one indicate that efforts are greater than expected rewards, indicating a stressful condition at work (Siegrist, 1996; Niedhammer et al., 2004). Education was measured in total years of education. Socioeconomic status was reported and classified as manual (semi-skilled and unskilled manual occupations), non-manual (clerical and skilled manual occupations), and upper non-manual (managerial and professional occupations).

3.2.5 Stressful life events and emotional distress (Study V)

3.2.5.1 Stressful life events

Stressful life events (SLEs) were measured with the Social Readjustment Rating Scale (Holmes & Rahe, 1967), which has also been used in studies of LQTS patients (Hintsa et al., 2010a). The questionnaire included several different SLEs, such as death of a close person and serious illness of a family member; respondents reported whether he or she had experienced an SLE in the past 12 months, as well as the stressfulness of the
SLE (1 = not very stressful, 2 = intermediately stressful, 3 = extremely stressful). The SLE scale was dichotomized with an additional variable estimating the stressfulness of the life event that occurred. Those participants who reported experiencing (in the past 12 months) intermediately (2) or extremely (3) burdening SLE were coded as having encountered a burdening stressful life event (1 = at least one recent burdening SLE). Those who reported experiencing no stressful life event in the past 12 months or had rated their SLE as ‘not very stressful’ were grouped as having encountered no burdening SLE (0 = no recent burdening SLE).

3.2.5.2 Emotional distress

Emotional distress was assessed with three items from the Cope questionnaire (Carver et al., 1989): “I get upset and let my emotions out.”, “I get upset and am really aware of it.” and “I feel a lot of emotional distress and I find myself expressing those emotions a lot.” The response scale ranged from one to four (“does not describe me at all” = 1 to “describes me well” = 4). The reliability estimate of the scales was 0.71 (Cronbach’s alpha) for the LQTS mutation carriers.

3.3 Statistical analyses

3.3.1 Study I

The association of the three temperament traits (NS, HA and RD) with symptom status was tested with the analysis of covariance, with temperament traits serving as the dependent variables, with sex and group or symptom status serving as fixed factors, and a centred variable of age serving as a covariate. First symptomatic with asymptomatic LTQS mutation carriers were compared with each other on temperament characteristic, and then all LQTS mutation carriers were compared with the general Finnish population (YFS).
3.3.2 Study II

Differences in BIS were analysed using analysis of covariance with group (general population sample or LQTS mutation carriers sample), symptom status or mutation subtype as fixed factors. All analyses were adjusted for age and sex. Adjustment for sex is justifiable, as sex differences in BIS have been reported (Corr, 2004). First, symptomatic and asymptomatic LQTS mutation carriers were compared in BIS, and then all LQTS mutation carriers were compared to the general Finnish population (YFS). In an analysis that included only LQTS mutation carriers, LQTS mutation subtypes LQTS1, LQTS2 and LQTS3 were compared to each other.

3.3.3 Study III

All the comparisons in stressful work involvement were conducted with analysis of covariance. Sex served as the fixed factor and age as a covariate in each of the analyses; thus, all the analyses were adjusted for sex and age. In addition, depending on the analysis underway, group (general population sample or LQTS mutation carriers sample) and symptom status (arrhythmic or not) served as fixed factors. First means of stressful work involvement were compared in symptomatic and with asymptomatic LQTS mutation carriers. Then both symptomatic and asymptomatic LQTS mutation carriers were compared separately to the general Finnish population (YFS).

3.3.4 Study IV

Logistic multinomial regression analysis was used to compare symptomatic and asymptomatic LQTS mutation carriers with relative control subjects and with the general Finnish population (YFS) in their job strain and effort-reward imbalance. Binary logistic regression analyses served to compare the levels of job strain and effort-reward imbalance among symptomatic LQTS mutation carriers to those of asymptomatic LQTS mutation carriers. The analyses were adjusted for age, sex, education and occupation.
3.3.5 Study V

Analysis of covariance with linear trends was used to compare symptomatic and asymptomatic LQTS mutation carriers. The first model included the occurrence of burdening SLEs in the past 12 months and symptom group, sex, and age were used as covariates. Interactions were also analysed. Analysis of variance was also used to analyse continuous variables among the excluded vs. included participants.

3.3.6 Software details

All analyses were conducted with SPSS 15.0 for Windows and PASW Statistics 17.0 or 18.0.2. programs.
4 RESULTS

4.1 Temperament and LQTS

4.1.1 Cloninger’s TCI and LQTS (Study I)

On average, the LQTS mutation carriers were 41.5 years and the YFS participants, 37.6 years old (p < 0.001). Symptomatic LQTS carriers were on average 42.5 years and asymptomatic carriers 40.6 years old (p < 0.05). Of the LQTS mutation carriers, 64.4% were women, whereas 58.9% of the YFS participants were women (p < 0.05). Among the symptomatic mutation carriers, 73.7% were women, and of the asymptomatic carriers, 57.0% were women (p < 0.001). Of the 425 LQT1 mutation carriers, 180 were symptomatic, and of the 145 LQT2 mutation carriers, 76 were symptomatic; of the 17 LQT3 mutation carriers, 3 were symptomatic. Age and sex were controlled in all analyses. In the comparison of symptomatic to asymptomatic LQTS mutation carriers, mutation subtype was additionally controlled in a separate analysis (results not shown).

In the first analysis, Cloninger’s temperament traits were compared between symptomatic vs. asymptomatic LQTS mutation carriers (Figure 2). The results of the analysis of covariance show that the symptomatic and asymptomatic mutation carriers showed no difference from each other in HA scores (p-values > 0.05). HA was significantly higher in women (F = 12.43, 2.82 versus 2.66, p < 0.001, η² = 0.021). In line with previous findings (Cloninger, 2004), these results confirmed that HA was unrelated to age.

In the second analysis, all (symptomatic and asymptomatic) LQTS mutation carriers were compared to the sample from the general Finnish population and it was found that the LQTS mutation carriers scored higher on HA than did the general Finnish population (F = 30.60, 2.77 vs. 2.61, p < 0.001, η² = 0.011) (Figure 3). The analysis revealed no significant main effect of age (p < 0.05) on HA. HA was significantly higher in women when comparing all of the LQTS mutation carriers to the general Finnish population (F = 45.77, 2.72 vs. 2.54, p < 0.001, η² = 0.017). However, LQTS mutation carriers showed no differences in their NS and RD scores from those of the general Finnish population.
No significant differences were found in HA subcomponents when comparing symptomatic and asymptomatic LQTS mutation carriers were compared to each other. LQTS mutation carriers scored higher in three subcomponents of HA than did the YFS population. It was found that the LQTS mutation carriers scored higher in anticipatory worry (2.59 vs. 2.46, p < 0.001, η² = 0.009), fear (3.24 vs. 3.04, p < 0.001, η² = 0.011) and fatigability (5.46 vs. 2.28, p < 0.001, η = 0.028), but no significant differences in shyness.

**Figure 2.** Comparison of asymptomatic to symptomatic LQTS mutation carriers.

*Note: Mean values and standard error of means presented.*
**Figure 3.** Comparison of LQTS mutation carriers to the general population.

*Note: Mean values and standard error of means presented.*
4.1.2 Gray's RST and LQTS (Study II)

The results revealed no significant differences in BIS temperament between the symptomatic and asymptomatic LQTS mutation carriers (3.27 versus 3.24, p > 0.05). The mean BIS score was higher in LQTS mutation carriers than in the general Finnish population (F = 9.13, 3.25 vs. 2.99, p = 0.003, \( \eta^2 = 0.014 \)) (Figure 4). There were no significant differences in BIS between the different mutation subtypes, which had mean values of 3.22, 3.20 and 3.40 for the LQTS1 (n = 421), LQTS2 (n = 145) and LQTS3 (n = 17) mutation carriers, respectively. In this sample, women scored higher in BIS than did men (F = 11.3, 3.32 vs. 3.06, p < 0.001, \( \eta^2 = 0.017 \)).

Figure 4. Mean scores of behavioural inhibition with standard errors of means.
4.2 Stressful work involvement and LQTS (Study III)

Symptomatic LQTS mutation carriers scored higher than did asymptomatic LQTS mutation carriers (F = 8.818, 1.51 versus 1.40, p = 0.003, $\eta^2 = 0.022$) and the general Finnish population (F = 18.187, 1.51 vs. 1.39, p < 0.001, $\eta^2 = 0.012$) in stressful work involvement (Figure 5). On the other hand, asymptomatic LQTS mutation carriers showed no difference from the general Finnish population in stressful work involvement (F = 0.790, 1.40 vs. 1.39, p = 0.374, $\eta^2 < 0.001$). When added to the model, LQTS subtype failed to account for stressful work involvement.

**Figure 5.** Mean values for stressful work involvement with standard errors of means.
4.3 Work stress and LQTS (Study IV)

Analyses controlling for age, sex, education and occupation showed an association of the symptomatic status of LQTS with higher job strain (OR 1.72, 95% CI 1.27 to 2.34, p = 0.001) and greater effort-reward imbalance (OR 3.92, 95% CI 1.66 to 9.24, p = 0.002) than for control subjects (Table 2). It was found that of the work characteristics, higher job demands (OR 1.72, 95% CI 1.16 to 2.57, p = 0.007), lower job control (OR 0.46, 95% CI 0.46 to 0.99, p = 0.046), and lower rewards at work (OR 0.59, 95% CI 0.40 to 0.86, p = 0.007) associated with the occurrence of symptoms in LQTS independently of age, sex, education and occupation compared to relative control subjects. Controlling additionally for the use of beta-blockers did not markedly change the results. Asymptomatic LQTS mutation carriers showed no differences from control subjects in job demands/effort, job control or rewards at work.

Table 3 presents binary logistic regression analyses comparing symptomatic and asymptomatic LQTS mutation carriers. Analyses controlling for age, sex, education and occupation showed a stronger association of high job strain (OR 1.52, 95% CI 1.06 to 2.17) and high effort-reward imbalance (OR 5.66, 95% CI 1.75 to 18.27) in LQTS mutation carriers with arrhythmic events than in LQTS mutation carriers with no arrhythmic events. Controlling additionally for the use of beta-blockers did not markedly change the results. Comparisons of symptomatic LQTS mutation carriers with asymptomatic LQTS mutation carriers, revealed that lower rewards at work (OR 0.59, 95% CI 0.37 to 0.95, p = 0.031) were related to the occurrence of LQTS symptoms.

Because previous studies had found stress-related differences between the general Finnish population and LQTS mutation carriers, symptomatic and asymptomatic LQTS mutation carriers were compared to the controls comprising the YFS subjects in job strain and effort-reward imbalance. Table 4 presents the results of multinomial logistic regression. Analyses controlling for age, sex, education and occupation showed an association of higher job strain (OR 1.51, 95% CI 1.13 to 2.02, p = 0.006) and higher effort-reward imbalance (OR 1.86, 95% CI 1.00 to 3.46, p = 0.049) in symptomatic LQTS mutation carriers than in the YFS control subjects, but not in asymptomatic LQTS mutation carriers.
Table 2. The results of multinomial logistic regression analyses comparing the level of work stress of symptomatic LQTS patients and asymptomatic LQTS mutation carriers to that of control subjects.

<table>
<thead>
<tr>
<th>JOB STRAIN</th>
<th>EFFORT-REWARD IMBALANCE</th>
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<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>1.68</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>1.12</td>
</tr>
<tr>
<td>Control subjects</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>1.72</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>1.18</td>
</tr>
<tr>
<td>Control subjects</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>1.72</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>1.18</td>
</tr>
<tr>
<td>Control subjects</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Controlled variables. Model 1: age, sex; Model 2: age, sex, education and occupation; Model 3: Model 1 and 2 + beta blocker therapy.

Symptomatic LQTS patients n=70; Asymptomatic LQTS mutation carriers n=103; relative control subjects n=203. Control subjects=relative controls.

Table 3. The results of binary logistic regression analyses comparing the level of work stress of symptomatic LQTS patients to that of asymptomatic LQTS mutation carriers.

<table>
<thead>
<tr>
<th>JOB STRAIN</th>
<th>EFFORT-REWARD IMBALANCE</th>
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<tr>
<td></td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
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<tr>
<td>Symptomatic LQTS</td>
<td>1.57</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>1.00</td>
</tr>
<tr>
<td>EFFORT-REWARD IMBALANCE</td>
<td>Model 1</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>6.14</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Controlled variables. Model 1: age, sex; Model 2: age, sex, education and occupation; Model 3: Model 1 and 2 + beta blocker therapy.

Table 4. The risk for high work stress among symptomatic and asymptomatic LQTS mutation carriers compared to that of YFS control subjects.

<table>
<thead>
<tr>
<th>JOB STRAIN</th>
<th>EFFORT-REWARD IMBALANCE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>1.51</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>0.98</td>
</tr>
<tr>
<td>YFS control subjects</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Symptomatic LQTS patients n=70; Asymptomatic LQTS mutation carriers n=103; YFS control subjects n=1340

Controlled variables: age, sex, education and occupation.
4.4 Emotional distress and stressful life events (Study V)

Higher emotional distress was related to younger age \((p = 0.002)\), and emotional distress was higher in females \((p = 0.001)\) and in those who had recently (12 months) experienced stressful life event (SLE) \((p = 0.001)\). There was no difference in emotional distress between symptomatic and asymptomatic mutation carriers \((p = 0.270)\), but there was an interaction between LQTS symptom status and recent SLEs \((p = 0.017)\), indicating that the association between SLEs and emotional distress was stronger in symptomatic mutation carriers \((\beta = 0.35, p < 0.001)\) than in asymptomatic mutation carriers \((\beta = 0.13, p = 0.393)\). The interaction effect is further illustrated in Figure 6.

Adjusting the usage of beta-blockers or mutation subtypes did not affect the results. Beta blockers showed no relationship with emotional distress \((p = 0.803)\), and there were no differences between mutation subtypes (LQTS1, LQTS2, and LQTS3) in emotional distress \((p = 0.733)\).

Figure 6. Emotional distress in symptomatic and asymptomatic carriers with and without a recent burdening stressful life event. Error bars show 95% confidence intervals.
5 DISCUSSION

The study was set up to investigate what causes symptoms in the long QT syndrome, a congenital heart disease. The results suggest that the symptoms occur as a result of a combination of innate stress-related traits and environmental stress loading. Stress proneness and the influence of environmental stress on LQTS were examined.

LQTS mutation carriers appeared to have higher stress proneness in terms of HA and BIS temperament than did the general population, but symptomatic and asymptomatic LQTS mutation carriers did not differ from each other. Symptomatic LQTS mutation carriers had higher stressful work involvement and higher work stress in both job-demands-control and effort-reward imbalance models, than did the asymptomatic. In addition, the symptomatic LQTS mutation carriers had higher emotional distress after a stressful life event (SLE) in a 12-month period, than did the asymptomatic LQTS mutation carriers. Thus, symptoms will occur more likely if the environmental stress load is high. Surprisingly, none of the LQTS mutation subtypes (LQTS1, LQTS2, LQTS3) showed any differences in the variables studied.

5.1 Temperamental stress proneness

5.1.1 Harm avoidance and LQTS

HA was equally high among all LQTS mutation carriers regardless of their symptoms. They seemed to be higher in HA (i.e. stress proneness) than the YFS general population.

HA has been associated with both physiological (Puttonen et al., 2008) and psychological (Puttonen et al., 2005; Ravaja et al., 2006) stress proneness. HA is also related to sensitivity to SLEs (Gothelf et al., 2004). Previous research on the present sample has shown that symptomatic LQTS mutation carriers experienced significantly more SLEs than did asymptomatic mutation carriers (Hintsa et al., 2010a).

HA is also strongly associated with depressive mood (Farmer & Seeley, 2009) and depression (Richter et al., 2000; Cloninger et al., 2006; Celikel et al., 2009) which in turn has been linked to the risk for ventricular arrhythmias (Watkins et al., 2006), while studies have shown depressive symptoms to be related to increased arrhythmic risk.
among LQTS mutation carriers in the very same sample as the one studied here (Hintsa et al., 2009). Accordingly, a high level of HA may predispose a person to depression, which in turn decreases the ability to cope with stress and increases the likelihood of LQTS symptoms.

5.1.2 Behavioural inhibition and LQTS

The results with BIS were similar to those with HA: asymptomatic and symptomatic LQTS mutation carriers exhibited similar stress-proneness when measured with BIS, and their BIS was higher than that of the YFS general population. BIS has been linked to higher emotional sensitivity to stressors (Heponiemi et al., 2003), reactions to SLEs (Gable et al., 2000), and higher heart rate and reduced parasympathetic activity (Keltikangas-Järvinen et al., 1999). Individuals with high levels of BIS activity are likely to react more strongly to stressful situations and experience even milder situations as more stressful, thus yielding a result that resembles the result with HA.

5.1.3 Differences in HA and BIS as a measure of stress proneness

In regard to the differences between HA and BIS, BIS measures the effect of motivational context in behaviour, i.e. the predictability and learning of aversive and appetitive responses (Torrubia et al., 2008). The BIS scale is designed to measure the type of situations that a person experiences as anxiety, rather than how often the person experiences anxiety (Jorm et al., 1998). This may be an important distinction, because people may learn to avoid negative situations and emotional states through coping mechanisms.

An additional difference between HA and BIS is that the latter is more closely related to punishment: by definition, BIS involves mechanisms that are sensitive to conditioned aversive stimuli in the environment (Corr, 2004). Thus, BIS explicitly involves low-level learning mechanisms, whereas HA could be viewed as involved with fatigability, shyness and fear of uncertainty (i.e. general features not necessarily involving conditioned negative responses). Thus, therapies that involve learning could more directly affect behaviour and emotional outcomes in patients with high BIS.
the other hand, Cloninger’s theory (Cloninger et al., 1993) predicts that although modifying a high HA is almost impossible, developing character traits that will modulate the outcome of a high-HA is possible (i.e. high HA persons who will not develop typical adverse health outcomes such as depression by having high self-directedness). It is true that the same sample of LQTS mutation carriers had both high BIS and high HA, but measuring both HA and BIS nevertheless provides a deeper understanding of stress proneness: their stress proneness, which covers BIS also, which itself measures conditioned responsivity to aversive stimuli, is wider than previously thought (Corr, 2004).

### 5.2 Stressful work involvement

The results suggest that stressful work involvement is related to symptomatic status in LQTS. Symptomatic LQTS mutation carriers had higher stressful work involvement than did asymptomatic LQTS mutation carriers, who in turn, showed no difference from the general Finnish population. Thus, high stressful work involvement (i.e. worrying about work and job dissatisfaction) may be linked to a higher risk for arrhythmic events. The results may imply that individual stress proneness related to work, but independent from their temperaments (HA and BIS), might be a potential risk factor for arrhythmias in LQTS.

Stressful work involvement – derived from questions measuring parts of type A behavior – is thought to reflect an individual response style to stressors in the workplace, rather than a feature of the workplace itself. Thus, taking into account the equal temperamental stress proneness (HA and BIS) of the symptomatic and asymptomatic LQTS mutation carriers, the result is somewhat surprising. It seems that this stress-related feature is evident only in the workplace context (i.e. it is a very narrow stress marker). It is also possible that stressful work involvement measures the stress in the workplace itself – i.e. the same as what work stress measures are designed to measure.
5.3 Work stress

Purpose of using work stress measurements in the study was to examine the working environment as independently as possible from personal experience or individual interpretation (i.e. unlike other measures, which were developed either to capture primarily personal stress proneness (temperaments HA and BIS) or to measure an individual’s stress reactivity, responses or styles in certain stressful contexts (stressful work involvement, emotional distress after recent SLEs)).

It was examined whether job strain and effort-reward imbalance, as well as their components (job demands/effort, job control, rewards at work) associated with symptom status in LQTS. We found that higher work stress indexed by job strain and effort-reward imbalance associated with the occurrence of symptoms in LQTS. Of the components of job strain and effort-reward imbalance, higher job demands, lower job control and lower rewards at work all related to person’s previous history of LQTS symptoms. In addition, the symptomatic, but not the asymptomatic LQTS mutation carriers differed from the YFS general population in both job strain and effort-reward imbalance.

Higher job strain was associated with history of LQTS symptoms independently of age, gender, education and occupation, and taking beta-blocker medication into account in the analyses did not attenuate the association. Previous evidence has shown that job strain is a major risk factor for cardiovascular disease (Belkic et al., 2004; Steptoe & Kivimäki, 2012), and job strain has been associated with a significantly higher risk for recurrent CHD events (Aboa-Eboule et al., 2011). The present results add to the literature by showing an association between job strain and the risk for arrhythmias in LQTS.

Compared to relative control subjects, lower job control associated with symptomatic LQTS when adjusting for age, sex, education and occupation, but this association became non-significant when beta-blocker treatment was taken into account. There was, however, no significant difference between symptomatic and asymptomatic LQTS mutation carriers in their job control.

It was also found that higher effort-reward imbalance associated to the occurrence of symptoms in LQTS. Effort-reward imbalance was 3.3-fold higher among symptomatic
LQTS mutation carriers than among their non-affected relatives, and over 5-fold higher than among asymptomatic LQTS mutation carriers. These findings are in line with those of a previous study showing that effort-reward imbalance at work is positively associated with the occurrence of coronary events (van Vegchel et al., 2005).

5.4 Stressful life events and emotional distress

It was examined whether encountering a highly burdening recent stressful life event (SLE) is related to higher emotional distress in symptomatic LQTS mutation carriers. The results indicated that symptomatic LQTS mutation carriers had higher emotional distress after a recent intermediately to highly burdening SLE. This may imply that symptomatic LQTS mutation carriers experience greater emotional distress than asymptomatic LQTS mutation carriers when encountering highly burdening SLEs.

These findings imply that symptomatic LQTS mutation carriers are sensitive to SLEs in terms of high emotional distress. As the studies in HA and BIS suggested, LQTS mutation carriers are more stress prone than the general population in terms of temperament, which may amplify perceived stress (Heponiemi et al., 2003).

Previous studies on the same sample have shown that symptomatic LQTS mutation carriers have encountered more SLEs in their lives than did asymptomatic LQTS mutation carriers (Hintsa et al., 2010a). Encountering SLEs requires the ability to efficiently relieve stress. Negative emotional arousal expresses maladaptive emotional stress (Lazarus & Folkman, 1984) and may reduce one’s ability to successfully manage acute stress. It may also be relevant to note that negative emotionality has been related to SLEs (Elovainio et al., 2007). This study provided new information on a potential risk factor in LQTS (i.e. an interaction between SLEs and emotional distress).

It is also possible that some innate differences between symptomatic and asymptomatic LQTS mutation carriers exist in some narrowly defined stressful contexts. These differences between the symptomatic and asymptomatic LQTS mutation carriers are not reflected in the HA and BIS scores which suggested equal stress-proneness between symptomatic and asymptomatic LQTS mutation carriers.

One possible explanation for the greater emotional distress that the symptomatic LQTS mutation carriers experienced would be that they in fact faced more serious life
events, a fact that the questionnaire would (likely) have missed even though asking about the seriousness of the life event. This would mean that the difference in emotional distress would completely be an environmental effect and not a systematic response style of the symptomatic LQTS mutation carriers.

5.5 Stress in LQTS mutation carriers and biological stress mechanisms

The biological basis of stress reactions among LQTS mutation carriers is relevant for many reasons. The primary reason is that without a detailed biological understanding of the ongoing stress reactions among symptomatic and asymptomatic LQTS mutation carriers, the causal chain of events leading from perceived environment to the arrhythmias will be lacking.

The biological basis of the psychological phenomena studied in this dissertation can be described on many levels. For instance, the neurotransmitter systems or brain areas involved may be important, and the functioning of the autonomic nervous system and the HPA axis are also relevant. Other considerations of the biological background are also relevant and are discussed when suitable research is available on the topic.

5.5.1 Temperamental stress proneness and biological basis

There is some research that has suggested links between different temperament traits and neurotransmitters, but much of the evidence about the neurotransmitter systems behind stress proneness is not comprehensive. On the other hand, evidence about the role of biological stress systems (the autonomic nervous system and HPA axis) behind stress reactivity has been growing. This is also true for the relationship between stress and cardiovascular disease (Hintsanen et al., 2005; Kivimäki et al., 2007; McEwen & Stellar, 1993; Räikkonen et al., 1996).
5.5.1.1 Harm avoidance and biological basis

In Cloninger's psychobiological model of temperament, individual differences in HA are based on the activity of the serotonin system, with high HA associating with low serotonergic activity (Cloninger, 1987). Animal studies have shown an association between serotonergic system activity and HPA axis activity (Heisler et al., 2007). Further, lower saliva cortisol awakening response has been associated with lower HA (Rademaker et al., 2009) and changes in plasma cortisol with temperament (Tyrka et al., 2008). Other research has shown an association between high HA and low heart rate variability (low parasympathetic control) (Puttonen et al., 2008), which suggests low parasympathetic nervous system activation. Low parasympathetic cardiac control has proved harmful because it can lead to elevated risk for cardiac events (Tsuji et al., 1996) and ventricular tachycardia (Farrell et al., 1991).

5.5.1.2 Behavioral inhibition and biological basis

The biological bases of BIS and HA are somewhat similar as they both reflect stress proneness; research has suggested that BIS (like HA) is especially linked to the neurotransmitter serotonin (Gray, 1972, 1991). The question whether specific genes lead to higher BIS or HA in LQTS mutation carriers remains unanswered. The mutations in the genes linked to LQTS could be expressed elsewhere in the body, including the central nervous system. For example, the HERG (KCNH2) gene, which is related to LQTS2, is expressed in the brain, and some mutations in the gene have been associated with brain alterations, which may lead to lower IQ and schizophrenia (Huffaker et al., 2009). BIS has also been shown to be higher in schizophrenia patients (Scholten et al., 2006). The genes related to both high BIS and LQTS could also appear at higher frequencies in the same areas inside Finland, or these genes could share a linkage disequilibrium (i.e. they would be physically close to each other in the same chromosomes or for some other reason appear together in the same persons). Thus, the real underlying reason for the association between the LQTS mutation genes and high BIS remains unclear.
5.5.2 Work stress and biological basis

The biological basis of work stress has been studied on the level of the autonomic nervous system and HPA axis activity.

Our finding linking lower job control with potential arrhythmic risk is in accordance with previous findings on job control, altered autonomic function and baroreflex sensitivity. Thus, studies have previously shown that those with lower job control have lower diastolic baroreflex sensitivity (Thomas et al., 2004) and reduced cardiac vagal control (Collins et al., 2005).

Higher effort-reward imbalance has previously shown a link to lower vagal (i.e. parasympathetic) cardiac control (Hanson et al., 2001; Vrijkotte et al., 2000). Higher effort-reward imbalance has shown an association with reduced parasympathetic activity in samples comprising only or mainly women (Hintsanen et al., 2007; Uusitalo et al., 2011), but not in men (Hintsanen et al., 2007). Previous studies have reported odds ratios ranging from 1.22 to 8.98 for the association between high effort-reward imbalance and elevated risk for CVD incidence (van Vegchel et al., 2005) that are in accordance with the odds ratios found in the present study.

Lower rewards at work associated with symptomatic LQTS status, which is in line with the results of previous studies reporting an association between lower rewards at work and higher heart rate and reduced vagal activity (Hintsanen et al., 2007), and between lower rewards and elevated risks for recurrent coronary heart disease events among workers who had returned to work after their first myocardial infarction (Aboa-Eboule et al., 2011). A population-based sample has shown that lower rewards at work is also associated with higher heart rate and reduced vagal activity, but showed no association between effort and cardiac measures (Hintsanen et al., 2007). The present study showed a relationship between lower rewards at work and symptom status in LQTS.

Reduced capacity for cardiac vagal control may play a major role in elevating the risk arrhythmic events among LQTS patients under stress. Job strain has previously associated with pathogenic cardiovascular regulation (Collins et al., 2005). Vagal tone is the primary influence in cardiovascular recovery, and vagal rebound is associated with changes in baroreflex sensitivity (Mezzacappa et al., 2001). In a study by Collins et al.
(2005) of healthy men, it was observed the high-strain group showed elevated sympathetic and reduced vagal activity during workday. Job strain has also been related to greater systolic pressure responses to phenylephrine, which mimics the effects of noradrenaline, whereas lower job control associated with higher levels of plasma noradrenaline (Ziegler et al., 1995; Thomas et al., 2004).

Lower values for baroreflex sensitivity, measured with the phenylephrine method, have been related to lower risk for life-threatening arrhythmias (Schwartz et al., 2008). This suggests that when strong autonomic reflexes result in rapid increases in heart rate (HR), the probability of arrhythmic events increases. Evidence shows reduced vagal cardiac control and variability in high strain job and exhausted subjects (Collins et al., 2005). High job strain subjects showed reduced vagal cardiac control capacity, and exhausted subjects exhibited even greater reductions in such capacity (Collins et al., 2005). Studies have been previously shown that symptomatic LQTS mutation carriers report more chronic stress, manifesting with a higher level of exhaustion, than do asymptomatic LQTS mutation carriers (Hintsa et al., 2010a). Because both higher exhaustion and higher job strain are related to suppressed parasympathetic activity and control of the heart rate (Collins et al., 2005), LQTS mutation carriers with high job strain could be at greater risk for arrhythmias due to individual and environmental loading. Of the work characteristics, symptomatic LQTS patients had experienced higher job demands/effort at work than did relative control subjects and asymptomatic LQTS mutation carriers. The association between job strain and occurrence of symptoms in LQTS seems to stem mainly from higher job demands rather than from lower job control because job demands were more strongly associated with the symptomatic status of LQTS. This result differs from those of previous studies reporting no association between job demands and the parasympathetic nervous system, or between job demands and baroreflex sensitivity (Collins et al., 2005; Thomas et al., 2004).

5.5.3 Emotional distress and biological basis

Based on the existing literature, emotional distress in its different forms (i.e. intense feelings and expression of negative emotions) may be maladaptive for health.
(Keltikangas-Järvinen et al., 1996; Siegman & Snow, 1997; Vitaliano et al., 1993) and is related to the functioning of autonomic nervous system (Dikecligil et al., 2010) and to higher levels of cortisol (Abercrombie et al., 2005). The finding for emotional distress may be generalisable to different stress contexts and may also apply to stressful work involvement.

5.5.4 Psychological stress, ANS and HPA

HA, BIS, emotional distress, stressful work involvement, work stress and stress in general may display its effect via altered cardiac stress reactivity (more sympathetic or less parasympathetic nervous system activity) or the overreactivity of the HPA axis. Thus, all of the different stress-related measures likely exhibit some similar biological background features.

High levels of cortisol have shown an association with cardiac events (Yamaji et al., 2009) and low parasympathetic control of the heart rate has shown an association with ischemic cardiac events (myocardial infarction, angina pectoris, death from coronary heart disease) and congestive heart failure (Tsuji et al., 1996). In addition, low parasympathetic control measured by heart rate variability has shown an association with elevated risk for ventricular tachycardia in post-infarction patients (Farrell et al., 1991). Sympathetic stimulation may prolong the QT interval and trigger arrhythmic events in LQTS (Morita et al., 2008).

In general, enhanced sympathetic stimulation is proarrhythmic and enhanced parasympathetic activity is protective with the exception of LQTS3 in which the arrhythmias typically arise during rest or sleep, i.e. under high parasympathetic control and low heart rate (Schwartz, 1984). Depressed vagal responsiveness was a risk factor for ventricular fibrillation during exercise-induced increased sympathetic activity (Rovere et al., 1998). Further information on emotional and biological mechanisms leading to arrhythmias can be found in a review by Taggart and colleagues (2011).
5.6 Methodological considerations

The study was based on data from self-reported questionnaires and shares the strengths and weaknesses of self-reported studies. Also, utilising a cross-sectional rather than a longitudinal design (at this point of the study) may hamper causal implications.

A correlative and cross-sectional study cannot prove causality. Indeed knowledge about the syndrome may itself raise the one’s likelihood to perceive challenges as stress. Thus, identifying the stress-related physiological mechanisms that may differentiate symptomatic and asymptomatic LQTS mutation carriers would require experimental settings. In addition, a longitudinal design would be useful in understanding more about the causality of stress and LQTS.

To assess stressful work involvement, we used a scale derived from the Framingham type A questionnaire. The general validity of this scale is unknown, however, which is a limitation of the study. Furthermore, although the measure assesses individual stressful work involvement, it is unable to distinguish the reasons for these perceptions (i.e. whether they are related solely to individual stress proneness or to actual stressors in the job).

One limitation is the fact that it is difficult to know whether the questions used to measure emotional distress measured a tendency to react in a certain emotional way which was more visible after stressful life events. It is possible that the answers reflect a certain response style, and if so, the interpretation of the results for emotional distress is more difficult. It is puzzling how and why would a response style correspond with symptom status after an SLE, especially when symptomatic and asymptomatic LQTS mutation carriers have equal stress proneness when measured by HA and BIS.

Another limitation is a potential bias due to non-response to the work stress questionnaire. Persons who failed to respond may have been uninterested in participating because they experienced no stress at work. However, it is equally likely that persons who failed to respond were unable to respond because they experienced too much stress at work. Furthermore, using a proxy measure for effort-reward imbalance may have influenced the findings. Rewards at work are measured in a more versatile way in the original measure of effort-reward imbalance, and each measure consists of several items whereas the proxy measure used in the present study measured rewards at
work only with three items. The reliability of the reward scale, however, was within an acceptable range. It is recommended to use the original effort-reward imbalance measure in the future studies whenever possible. Work stress was measured with two work stress questionnaires which have been widely validated in cardiovascular research and which reflect two of the most well-known work stress models.

Although age was controlled for in all of the analyses, it is worth noting that the LQTS mutation carriers were 10 years older on average than the participants from the general Finnish (YFS) population.

A special strength of the study is the availability of the very comprehensive population-based databases for both the general Finnish population and a large sample of DNA-documented LQTS patients in Finland.

5.7 Conclusions and practical implications

Future research on the topic of links between stress and symptoms or arrhythmias in LQTS should include possibly the following: follow-up studies, laboratory studies that allow causal implications, the possibility to replicate the results in other countries, and a rigorous effort to calculate a combined risk score for arrhythmic events, in LQTS mutation carriers and their environmental stress. Effort for stress-reducing interventions in LQTS mutation carriers should be also taken into consideration.

The clinical importance of the present study comes largely from the finding that higher work stress is related to the risk for arrhythmic events in LQTS. Experiencing chronic stress at work may alter autonomic nervous system function, in particular suppress parasympathetic activation, and may also prevent LQTS mutation carriers from relaxing after work or during days off. Although this process may eventually lead to fatigue or exhaustion, it may also increase the healthy living habits of patients. Investigating work conditions during the clinical management of LQTS patients, if deemed as necessary, could prove beneficial. Accordingly, initiating stress interventions at work and referring patients to psychological assistance when needed may be important. Stress management interventions in the work place have been found to improve stress reactivity (Limm et al., 2011).
Our findings contribute to the literature on stress and LQTS by showing that environmental stress may elevate one’s risk for symptoms in LQTS. The clinical implications are that the present evidence may help in the risk assessment LQTS, and in counseling of LQTS patients. LQTS patients could benefit from learning how to manage SLEs efficiently and successfully, and by directing them to psychological counseling for additional emotional support if necessary.

Follow-up studies and laboratory studies are currently underway, and additional data from longitudinal designs and the laboratory will add considerably to our understanding of LQTS in general and of the role stress plays in arrhythmias in LQTS.
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