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Genetics of vasovagal syncope

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Abstract

Introduction: Vasovagal syncope (VVS) is the most frequent type of syncope and affects about 25% of the population. The role of genetic factors in VVS has long been debated. In this review we will discuss the current evidence that strongly suggest a major genetic component.

Clinical genetic studies: Family aggregation studies have consistently shown that individuals with VVS more frequently have affected family members with VVS than unaffected controls. Clear evidence for the relevance of genetic factors was provided by a twin study that showed significantly higher concordance rates in monozygous compared to dizygous twins for frequent syncope and syncope associated with typical vasovagal triggers. Analysis of the family history of the concordant monozygous twins revealed that complex inheritance is operative in the majority but rarer families with autosomal dominant inheritance also exist. Several autosomal dominant families have been described in the literature with the largest including 30 affected individuals.

Molecular genetic studies: Candidate gene association studies have so far been disappointing as they have revealed either negative or unconfirmed results. However, in an autosomal dominant family the first locus for VVS was identified on chromosome 15q26. The underlying gene has not been identified yet.

Conclusion: Genetic factors play a role in VVS. Most cases follow complex inheritance; autosomal dominant inheritance occurs less frequently. Identification of the underlying genes will improve our understanding of pathophysiology and may lead to new therapeutic strategies.

Introduction

Vasovagal syncope (VVS) is the most frequent type of syncope and affects about 25% of the population at least once during life (Chen et al., 2006; Ganzeboom et al., 2006; Thijs et al., 2006). VVS may lead to severe injuries and recurrent VVS reduces the quality of life (Rose et al., 2000; Santhouse et al., 2007). Therapeutic options for VVS are limited (Moya et al., 2009) and the development of new therapeutic strategies is hampered by the elusive pathophysiology (Mosqueda-Garcia et al., 2000).

The involvement of genetic factors in VVS has long been debated (Bizios et al., 2009; Olde Nordkamp et al., 2009) but current evidence strongly suggests a major genetic component. In this review we will discuss the clinical and molecular genetic findings in VVS.

Family aggregation studies

Family aggregation studies examine if affected individuals with a certain disease are more likely to have affected family members with this disease than healthy controls. A significant difference in the frequency of affected relatives is considered evidence for a genetic contribution to the disease of interest. Several family aggregation studies have been performed for VVS.

Camfield and Camfield reviewed the family history of 30 children with VVS and their unaffected best friends (Camfield et al., 1990). They found at least one affected first degree relative in 90% of patients as opposed to 33% of controls ($p < 0.01$). 37% of the patients had both an affected sibling and parent as compared to 4% of the controls ($p < 0.01$). The authors concluded that VVS may be multifactorially inherited involving both genetic and acquired factors (Camfield et al., 1990).

Another group examined 103 volunteers who developed VVS during exposure to blood or injury and 101 subjects without syncope and reported that 66% of subjects with syncope had

at least one parent with syncope compared to 41% of non-fainting subjects (Kleinknecht et al., 1989). The difference was statistically significant ($p < 0.006$). In a follow-up study subjects were classified in different subgroups and it was reported that 94% of “essential fainters”, which were defined as probands with syncope who did not report fear or anxiety during exposure to blood or injury, had a family history of syncope (Kleinknecht et al., 1990).

Mathias et al. observed a family history of syncope in 51% of patients with tilt confirmed VVS as compared to 28% of suspected VVS with a negative tilt test result ($p < 0.05$, (Mathias et al., 1998). Interestingly, only 3% of patients with other types of neurally mediated syncope, mainly carotid sinus hypersensitivity, had a family history. The authors interpreted their findings as evidence for a multifactorial mode of inheritance in VVS including genetic and environmental factors (Mathias et al., 1998). Later on, Mathias et al. reported a family history in 81 (36%) of 227 cases with VVS (Mathias et al., 2001). Another study identified a family history of syncope in 19% of 441 patients with tilt confirmed VVS (Newton et al., 2003). Thirty-seven percent of the first degree relatives were affected. The authors also performed tilt table testing in 11 first degree relatives including four unaffecteds and observed abnormal responses in all of them. They discussed their results as evidence for a genetic contribution to VVS possibly on an autosomal recessive or complex mode of inheritance (Newton et al., 2003). Holmegard et al. observed a positive family history in 37 (50%) of 74 patients with VVS and tilt induced syncope (Holmegard et al., 2013a).

Serletis et al. evaluated 62 medical students and their families regarding VVS (Serletis et al., 2006) and found that syncope was more frequent in females (40%) than in males (25%). The probability of fainting by the age of 30 years was 34% for females and 10% for males if both parents were unaffected. This increased to 48% for females and 28% for males if one parent was affected and to 78% for females and 55% for males if both parents were affected. If the mother was affected the risk of developing syncope was increased threefold in offspring of

either sex but an affected father only increased the risk in male children. The reason for this sex-dependent transmission remains unclear but the authors suggested a possible epigenetic mechanism (Serletis et al., 2006).

In summary, family aggregation studies for VVS consistently showed that a family history of VVS was more frequent in probands with VVS compared to controls. However, other authors argued that the familial aggregation observed may have occurred by chance due to the high frequency of syncope in the general population (Olde Nordkamp et al., 2009). We think this is implausible as the evidence from multiple independent familial aggregation studies does support a genetic component to syncope.

Twin studies

Twin studies are a powerful method to detect the presence and contribution of genetic factors to a disease by comparing the concordances of monozygous and dizygous twins. Monozygous twins have virtually the same genomic DNA sequence. In contrast, dizygous twins share only 50% of their genomic DNA sequence like ordinary siblings. A twin pair is called concordant if both twins have developed the disease or feature of interest. As twins usually share the same environment, significant differences in the concordances between monozygous and dizygous twins are reasonably attributed to genetic factors.

The first analysis of syncope in a twin study occurred in a study examining fears associated with blood, injury or injection (Page et al., 1998). This study examined 659 twin pairs from the Australian Twin Registry. Syncope was assessed as a secondary parameter. Evidence for a genetic effect was only observed for syncope that occurred associated with exposure to blood, injury or injection. A genetic contribution to syncope unrelated to these triggers was not observed. However, syncope was not the focus of that study, frequency was not assessed and syncope was diagnosed by self-report, rather than verified by a professional interview.

These issues may have influenced the results. In the following years, a few monozygous twin pairs concordant for VVS were reported but not compared to dizygous pairs (Arikan et al., 2009; Marquez et al., 2005).

We performed a twin study with particular emphasis on the validity of the diagnosis and avoidance of ascertainment bias (Klein et al., 2012). The twin pairs were recruited through the Australian Twin Registry and occurrence of syncope was validated via a telephone interview using a standardized questionnaire and available medical records. Fifty one same-sex twin pairs where at least one had syncope were ascertained. The comparison for any syncope revealed a trend towards higher casewise concordance in monozygous than dizygous twins ($p=0.06$). Significant and strong effects were found when concordances were analyzed for fainting at least twice unrelated to external circumstances ($p=0.018$) and syncope associated with typical vasovagal triggers such as exposure to blood, injury, medical procedures, prolonged standing, pain or frightening thoughts ($p<0.001$). These results clearly indicate that genetic factors are relevant in syncope with typical vasovagal triggers but also if syncope occurs frequently independent of the triggers. In subjects with infrequent syncope due to strong external triggers, genetic factors appear to be less relevant.

We also assessed the affected status of 1st and 2nd degree relatives of the concordant monozygous twin pairs to evaluate the predominant mode of inheritance (Klein et al., 2012).

We focused on the concordant monozygous twin pairs at this group is enriched for genetic factors for syncope as indicated by the fact that these genetically identical individuals both developed syncope. However, it still represents an unbiased sample regarding the presence of a family history as the twin pairs were recruited through the registry independent of the presence of a family history.

Twelve of 19 concordant monozygous twin pairs reported sparse or no other affected family members which is most consistent with complex inheritance where multiple genes and

environmental factors play a role. In the other 7 pairs, multiple close relatives were affected consistent with complex or autosomal dominant inheritance. Our findings support complex inheritance as the predominant mode of inheritance. However, some rarer families may follow autosomal dominant inheritance.

Candidate gene association studies

The aim of candidate gene association studies is the identification of susceptibility genes for a disease of interest. Variants in susceptibility genes increase the likelihood for the development of a certain disease but are on its own not sufficient to cause the disease. Variants in multiple susceptibility genes and possibly additional environmental factors need to be present for the disease to develop (complex inheritance).

Candidate gene association studies are based on previous assumptions on the involvement of a particular gene in a disease of interest. The study then compares the frequency of a known and common polymorphism in this gene, for example a single nucleotide exchange, between a group of affected individuals and a group of unaffected controls. If the frequency of the examined polymorphism is significantly different between the groups, the polymorphism is regarded as being associated with the disease of interest. However, this does not imply that the examined polymorphism is causally related to the disease of interest. The reason for this is that the genome is separated in so-called haplotype blocks. These represent regions that are usually inherited together as they are usually not separated by chromosomal recombination ("linkage disequilibrium"). The examined polymorphism serves as a marker for its haplotype block. The causal variant may be located anywhere in this haplotype block even in a different gene.

Candidate gene association studies are particularly susceptible to ethnic imbalances between the disease and control groups as polymorphisms occur with different frequencies in different

populations. Therefore, consistent replication is required before an association is accepted as meaningful (Ott, 2004).

Table 1 provides an overview on the candidate gene association studies for VVS. There are a few studies reporting associations of certain polymorphisms with a positive tilt table test.

These polymorphisms were located in the α_{1A} adrenergic receptor gene (Hernández-Pacheco et al., 2014), the β_1 adrenergic receptor gene (Hernandez-Pacheco et al., 2008; Marquez et al., 2007), the adenosine A_{2A} receptor gene (Saadjian et al., 2009), the gene encoding the β_3 subunit of the human G protein (Lelonek et al., 2009b), the gene encoding the α subunit of the Gs protein (Lelonek et al., 2008b) and the endothelin 1 gene (Sorrentino et al., 2009).

However, these studies included only small numbers of patients and the associations could not be consistently replicated (Lelonek et al., 2008b; Lelonek et al., 2009a; Sorrentino et al., 2010). Therefore, the association of these variants with a positive tilt table test remains unclear.

A recently published study (Holmegard et al., 2013b) examined genes that are involved in the postsynaptic cardiac parasympathetic signaling pathway (*CHRM2*, *GNB1*, *GNG2*, *KCNJ3*, and *KCNJ5*). The frequency of identified variants was compared between a cohort of patients with VVS and positive tilt table test and a group of healthy blood donors. It was not specified if the occurrence of VVS was excluded in the control group. Of the examined genes only a variant in the gene *KCNJ5* was significantly more frequent in the patient cohort. The authors concluded that the examined genes do not play a major role in the pathogenesis of VVS. (Holmegard et al., 2013b). Further studies are required to clarify the role of *KCNJ5* variants in VVS.

In conclusion, candidate gene association studies have been disappointing as they have only revealed negative or unconfirmed results. This resembles the situation in other diseases such as epilepsy where it was realized that such studies have been underpowered to detect common

variants with the expected small effect sizes (Tan et al., 2004). Candidate gene association studies are also hampered by the fact that they require a prior hypothesis regarding the genes involved.

One way to overcome these issues are genome wide association studies (GWAS). These studies provide a hypothesis free approach to identify common variants that contribute to a disease of interest. However, they require large cohorts of the order of several thousand, or better, ten thousand or more patients and controls.

So far, no GWAS has been performed for VVS and such a GWAS may encounter certain methodological challenges. In particular, it may be difficult to assemble a control cohort of individuals without VVS, as VVS occurs in about 25% of the general population and existing control cohorts are unlikely to have been screened for the occurrence of VVS. It should also be noted that GWAS typically identify common variants which usually have a low effect size (Mullen et al., 2009). In addition to common variants it is likely that rare variants, which have larger effect sizes but occur in less than 1% of the population, contribute to VVS. To identify these rare variants other study designs using next generation sequencing technologies are required.

Studies in large families

Another way to study the genetic influences on a particular disease is to study multiplex families with several affected family members. Of particular interest are families where the segregation of the disease is consistent with monogenic inheritance.

Autosomal dominant inheritance is a form of monogenic inheritance where a mutation in only one copy of a gene of major effect is responsible for the development of the particular phenotype. Children have a 50% chance of inheriting the abnormal gene from an affected parent. The inheritance pattern is sex-independent.

However, not everybody with the abnormal gene will develop the disease. This is referred to as incomplete penetrance. Penetrance is defined as the likelihood of developing the disease of interest if the abnormal gene is present. Possible reasons for incomplete penetrance are the presence of a protective genetic background or environmental factors.

Furthermore, family members who do not have the abnormal gene may develop the disease of interest. These subjects are called phenocopies. The phenocopy rate is defined as the likelihood of developing the disease of interest if the disease gene is not present. The phenocopy rate is particularly high in VVS due to its frequency in the general population.

Several larger individual families with VVS consistent with autosomal dominant inheritance have been reported in the literature. Mathias et al. described a family with an affected father and four out of seven affected children (Mathias et al., 2000). Interestingly, none of the three adopted children had VVS. A larger three-generational family with VVS was published by another group (Newton et al., 2005b). All nine affected family members were tilt-positive but had a normal ECG and no autonomic dysfunction. As 60% to 100% of each generation were affected, including subjects of either sex, an autosomal dominant mode of inheritance was considered (Newton et al., 2005b). Márquez et al. described a two-generation family in which the father and his four children (three girls and one boy) had VVS and a positive tilt test (Marquez et al., 2005).

Another group published a large three-generational family with VVS and migraine (Daas et al., 2009). The frequency of syncope was unusually high as in the second generation three out of three and in the third generation eight out of nine family members were affected. Eleven out of 12 subjects with VVS also suffered from migraine and 11 of the 14 subjects with migraine had syncope. The authors suggested an autosomal dominant mode of inheritance in this family (Daas et al., 2009).

As our twin-family study (Klein et al., 2012) had also shown evidence for the existence of autosomal dominant VVS we aimed to recruit such families (Klein et al., 2013). Out of 44 recruited multiplex families with VVS six were consistent with autosomal dominant inheritance. The largest family comprised 30 affected individuals with VVS over three generations (figure 1). The other five families contained between 4 and 14 affected individuals. The affected individuals reported typical triggers of VVS including the sight of blood, injury, medical procedures, prolonged standing, pain and frightening thoughts. The relevant triggers for VVS varied considerably between the affected subjects within the families (figure 1) indicating that the underlying mutation predisposes the subjects to VVS but does not predispose to syncope associated with a particular trigger. The relevant triggers are likely to be modified by additional genetic or acquired factors. This observation suggests that the mutated gene is likely to be part of the pathophysiologic pathway shared by different vasovagal triggers. Potential parts of this common pathway could be brainstem centers controlling the sympathetic innervation of resistance vessels or peripheral mechanisms involved in the regulation of vascular tone. It is unlikely that the mutated gene is involved in a trigger-specific part of the pathway as different triggers were present in the affected individuals.

Using genome-wide linkage analysis in the largest family we established the first locus for VVS on chromosome 15q26 (LOD score 3.28, Klein et al., 2013). Four affected family members did not carry the chromosome 15q26 haplotype indicating that they were phenocopies. Linkage to the chromosome 15q26 region was excluded in the two next largest families suggesting that different genes may be relevant in these families. The underlying genes have not been identified yet.

Genetic architecture of VVS

The current evidence clearly indicates that genetic factors play a major role in VVS. Genetic factors are particularly important when syncope occurs frequently or is associated with typical vasovagal triggers such as exposure to blood, injury, medical procedures, prolonged standing, pain or frightening thoughts. Genetic factors are less relevant when syncope occurs in the setting of strong environmental triggers such as dehydration or intercurrent illness.

There is a complex inheritance pattern in most cases with VVS where multiple genes and probably also environmental factors play a role. However, an autosomal dominant form of VVS has also been described and does not appear to be rare.

We conceptualize the genetic architecture of syncope as a spectrum with predominantly genetic factors on one side and predominantly external factors on the other (figure 2). In subjects with frequent syncope or typical vasovagal triggers genetic factors are important although external factors play a role as well (complex inheritance). Genetic factors are most important in families with autosomal dominant VVS which are located on the left side of the spectrum. On the right side of the spectrum are subjects who only faint with strong environmental triggers such as severe dehydration or illness where genetic factors appear to be less relevant.

Conclusion

Current evidence demonstrates that genetic factors are relevant in VVS. It usually follows complex inheritance where multiple genes and probably environmental factors play a role. Less frequently VVS can be inherited in an autosomal dominant manner. Discovery of the underlying genetic determinants will help to improve our understanding of the pathophysiology and may lead to better treatment of subjects with frequent and disabling VVS in the future.

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Figure legends:**Figure 1:**

Pedigree of the large family of Irish origin with autosomal dominant vasovagal syncope and living members in Australia, Ireland, England and New Zealand. The triggers are indicated by the coloured circles and vary considerably between the different family members. Subjects without triggers shown were either unavailable for a direct interview or did not report/remember typical vasovagal triggers. Red: blood, injury, medical procedures; blue: prolonged standing; purple: pain; green: frightening thoughts. Reprint with permission from Wolters Kluwer (Klein et al., 2013).

Figure 2:

Conceptualization of the genetic architecture of syncope. The x axis shows the spectrum of syncope with predominant genetic factors on the left and predominant external factors on the right. The y axis shows the assumed frequency of the different forms. Syncope due to strong environmental triggers where genetic factors are less relevant is assumed to be most frequent. Autosomal dominant vasovagal syncope is least common.

Figure 1

Table 1: Candidate gene association studies in VVS

Study	Probands with syncope			Controls	Examined genes and result of association (+/-)
	all	tilt pos.	tilt neg.		
Newton et al., 2005a	165	165	0	0	- <i>ACE</i>
Marquez et al., 2007	50	33	17	0	+ <i>ADRB1</i> tilt test result
Lelonek et al., 2007	68	68	0	0	+ <i>GNB3</i> "typical vasovagal history"
Lelonek et al., 2008b	137	96	41	0	+ <i>GNAS1</i> tilt test result
Lelonek et al., 2008a	213	*	*	32	- <i>GNB3</i>
Hernandez-Pacheco et al., 2008	70	48	22	0	+ <i>ADRB1</i> tilt test result
Lelonek et al., 2009b	217	152	65	0	- <i>GNAS1</i> + <i>GNB3</i> tilt test result - <i>RGS2</i>
Sorrentino et al., 2009	107	58	49	208	+ <i>EDN1</i> tilt test result - <i>EDNRA</i>
Lelonek et al., 2009a	307	207	100	74	- <i>GNAS1</i> - <i>GNB3</i> - <i>RGS2</i>
Saadjian et al., 2009	105	52	53	121	+ <i>ADORA2A</i> tilt test result, number of syncopal episodes
Mudrakova et al., 2009	191	117	74	0	- <i>ACE</i> - <i>AGT</i> - <i>ATR1</i> - <i>SERT</i>
Lelonek et al., 2009c	214	145	69	40	+ <i>RGS2</i> number of syncopal episodes
Sorrentino et al., 2010	129	73	56	0	- <i>ADRA1A</i> - <i>ADRB1</i> - <i>ADRB2</i> - <i>DBH</i> - <i>GNB3</i> - <i>SERT</i>
Holmegard et al., 2013b	74	74	0	208	- <i>CHRM2</i> - <i>GNB1</i> - <i>GNG2</i> - <i>KCNJ3</i> + <i>KCNJ5</i> VVS with positive tilt test result
Hernández-Pacheco et al., 2014	89	89	0	40	+ <i>ADRA1A</i> tilt test result

Number of included probands and controls as well as studied genes are listed.

+ indicates that an association was found for the listed variable; – indicates that no association was found; * data not available.

ACE: angiotensin converting enzyme; *ADORA2A*: adenosine A_{2A} receptor; *ADRA1A*: α_{1A} adrenergic receptor; *ADRB1*: β_1 adrenergic receptor; *ADRB2*: β_2 adrenergic receptor; *AGT*: angiotensinogen; *ATRI*: angiotensin II receptor; *CHRM2*: muscarinic acetylcholine M2 receptor; *DBH*: dopamine beta hydroxylase; *EDN1*: endothelin-1; *EDNRA*: endothelin type A receptor; *GNAS1*: Gs protein α subunit; *GNB1*: G protein β_1 subunit; *GNB3*: G protein β_3 subunit; *GNG2*: G protein γ_2 subunit; *RGS2*: regulator of G-protein signaling 2; *KCNJ3*: potassium inwardly rectifying channel, subfamily J, member 3; *KCNJ5*: potassium inwardly rectifying channel, subfamily J, member 5; *SERT*: serotonin transporter

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