Introduction

Essential hypertension affects approximately 25% of individuals in Western societies, with an increased prevalence in older subjects. It has long been recognized that a significant part of the susceptibility for hypertension is inherited. However, unlike monogenic disorders, hypertension develops on the genetic background of multiple gene alterations in concert with environmental factors, e.g., nutrition and physical activity. The hunt for hypertension susceptibility genes is nourished from different aspects. One goal is easily understood: if a causative mutation or polymorphism is found, there exists, at least theoretically, the possibility to modify the activity of the gene product through existing or novel drugs. Moreover, since hypertension is not a disorder per se but a major risk factor for stroke, left ventricular hypertrophy, myocardial, and renal insufficiency, genetic testing could identify individuals at highest risk in order to provide them with optimized medical care to prevent the aforementioned sequels. Finally, one could envisage a scenario in which certain genotypes may be used to guide antihypertensive therapy in terms of drug class and dosage.

Enhanced G-Protein Activation in Hypertension

Our initial interest in the genetics of essential hypertension resulted from studies on hypertensive patients who as intermediate phenotypes displayed an increased activation of the Na/H exchanger in their blood cells [1]. This ion transport that is ubiquitously expressed serves intracellular pH control and sodium homeostasis. There were two hypotheses linking increased ion transport to hypertension: 1) increased activation of the ion transporter could result in enhanced renal sodium reabsorption, thereby potentially contributing to salt-sensitive hypertension or volume expansion; and 2) increased intracellular pH might favor growth processes, and thereby contribute to media hypertrophy in resistance vessels. Interestingly, increased Na/H exchanger activity persisted in immortalized blood cells from hypertensive subjects [2]. However, no mutation was found in the cDNA encoding NHE1, the gene encoding for this transporter. As these cell lines not only showed an increased ion transport but also proliferated distinctly faster than those obtained from normotensive controls with low Na/H exchanger activity, a thorough investigation into potential alterations in intracellular signal transduction processes located upstream of ion transport and growth control was initiated. It was found that lymphoblast cell lines with enhanced Na/H exchanger activity also displayed increased Ca$^{2+}$ signals and formation of inositol phosphates on stimulation of G-protein-coupled receptors [3]. Similar findings were made in primary skin fibroblasts from the same patients and controls [4]. Interestingly, when cells were pretreated with pertussis toxin, which prevents receptor activation of Gi/Go proteins, the enhanced signal transduction of "hypertensive" cell lines was normalized to that of "normotensive" cell lines. This led to the hypothesis of a genetically fixed enhanced G-protein activation in a group of patients with essential hypertension.

The G-protein β3 subunit (GNB3) C825T polymorphism was detected through a classical candidate gene approach using cell lines with enhanced G-protein activation from patients with essential hypertension. The 825T allele is associated with the expression of a shortened, functionally active splice variant of the G-protein β3 subunit and enhanced intracellular signal transduction. Independent studies have confirmed an association of the 825T allele with hypertension in whites. Potential pathogenetic mechanisms comprise an increased susceptibility for obesity in 825T allele carriers and, potentially, increased responsiveness to vasoactive hormones. Both phenomena appear to be strongly influenced by lifestyle in the sense of a gene-environment interaction. Whether hypertensive 825T allele carriers are at increased risk for stroke and left ventricular hypertrophy remains controversial. Current studies try to define optimal therapy strategies for hypertensive 825T allele carriers.
Function of G Proteins
G proteins are heterotrimers composed of α-, β-, and γ-subunits. They are predominantly localized at the plasma membrane and mediate the intracellular signal transduction by heptahelical receptors [5,6]. However, in contrast to what is generally known, G proteins are also involved in signal transduction process initiated by activation of receptors with intrinsic tyrosine kinase activity, e.g., receptors for insulin, insulin-like growth factor, and platelet-derived growth factors, to name a few. The βγ-dimers form a functional monomer and their composition of various βγ-subunit isoforms is essential for receptor–G-protein–coupling specificity. On receptor activation the α-subunit releases bound GDP in exchange for GTP, which causes the dissociation of α- and βγ-subunits. Both the α- as well as the βγ-subunits can inhibit or activate a variety of intracellular effectors including ion channels, phospholipases, adenyl cyclase isoforms, the phosphoinositide-3-kinase, the mitogen-activated protein kinase pathway, and so forth [7]. Due to the intrinsic GTPase activity the α-subunit hydrolyzes bound GTP to GDP, α- and βγ-subunits reassociate, and the complex is ready for the next activation cycle. Thus, G-protein activation is the bottleneck for intracellular signal transduction. Therefore, it is sensible to assume that mutations or genetic polymorphisms that affect G-protein function or expression have a strong impact on intracellular signal transduction, thereby modulating disease susceptibility, the natural course of disorders, and drug responses. There exist few examples for somatic and germ-line mutations in rare disorders.

The C825T Polymorphism: Part of a Complex Haplotype
Following systematic sequencing of genes encoding for G-protein subunits expressed in lymphoblasts and fibroblasts, Siffert et al. [9] detected a silent C825T polymorphism in exon 10 of the gene GNB3, which encodes the β3 subunit of heterotrimeric G proteins. The 825T allele was strictly associated with a truncated, albeit biologically active, splice variant of the Gβ3 protein generated through alternative splicing of exon 9 and was termed Gβ3s. Thus, in cells from homozygous 825C allele carriers only the wild-type protein or mRNA is expressed. In contrast, both homo- and heterozygous 825T allele carriers, show both the wild-type protein plus the shortened splice variant. Moreover, the 825T allele was strictly associated with enhanced G-protein activation [9]. It remained unresolved how a remote nucleotide exchange in exon 10 could affect splicing of exon 9, especially as these exons are separated by an intron of more than 1000 base pairs. Meanwhile, additional polymorphisms have been detected in the promoter and in intron 9, which, surprisingly, are in almost complete linkage disequilibrium as shown in Figure 1. These nucleotide exchanges define a complex “C-haplotype” and “T-haplotype” [10,11]. For practical reasons the C825T polymorphism can be used for genotyping due to its one-to-one coupling with the other frequent polymorphisms in GNB3.