Chapter 6

# Rho-kinase Gene Polymorphisms in Related Disease States

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Additional information is available at the end of the chapter

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**Abstract**

The Rho-kinase (ROCK) family members, consisting of ROCK1 and ROCK2, are serine-threonine kinases that are activated by small GTPases. ROCKs play central roles in the actin cytoskeleton organization and regulate a wide range of fundamental cellular functions, such as apoptosis, inflammatory responses, cell contractility, adhesion, migration, motility, proliferation, phagocytosis, and apoptosis. Accumulating evidence from basic and clinical studies supports the concept that ROCK plays important roles in many diseases and could be a potential therapeutic target for diverse disorders, including cardiovascular, neurologic, metabolic, autoimmune disorders, and cancers. Although there are only limited numbers of published studies related to *ROCK* polymorphisms in humans, the contribution of the genetic studies related to *ROCK* variants to the disease states is emerging. Identifying mutated genes or associated polymorphisms and evaluating their potential risks are important steps for understanding the genetic components and pathogenesis of diseases. Identification of functional mutations or polymorphisms could potentially help in the development of novel ROCK-specific therapies in related disease states.

**Keywords:** disorder, polymorphism, Rho-kinase, ROCK, variant

## 1. Introduction

Rho-kinase (ROCK) is a serine/threonine kinase that is activated by small Rho GTPase proteins. Two ROCK isoforms have been identified: ROCK1 and ROCK2. These ROCK isoforms are encoded by separate genes on human chromosomes 18q11.1 (ROCK1) and 2p24 (ROCK2). ROCK1 and ROCK2 enzymes contain 1354 and 1388 amino acids, respectively [1, 2]. Two isoforms have ~65% overall amino acid homology and ~92% homology in the kinase domain. The

carboxy terminus of ROCK folds back onto the kinase domain, thereby forming an autoinhibitory loop that maintains the enzyme in an inactive state. Binding of GTP-bound, biochemically active Rho (such as RhoA/RhoB/RhoC) to the Rho-binding domain (RBD) disrupts the negative regulatory interaction between the catalytic domain and the autoinhibitory C-terminal region, resulting in activation of the enzyme in response to extracellular signals [1, 2]. On the other hand, RhoE interacts with the N-terminal region of ROCK1 and prevents Rho binding to RBD [3]. ROCK1 is cleaved by caspase-3, but ROCK2 can be cleaved by granzyme B or caspase-2 (**Figure 1**) [1, 2]. ROCK enzymes are likely to exist as dimers by parallel association at the coiled-coil domain and the dimerized kinase domain of ROCK appears to be in an active conformation in the absence of phosphorylation [4, 5].

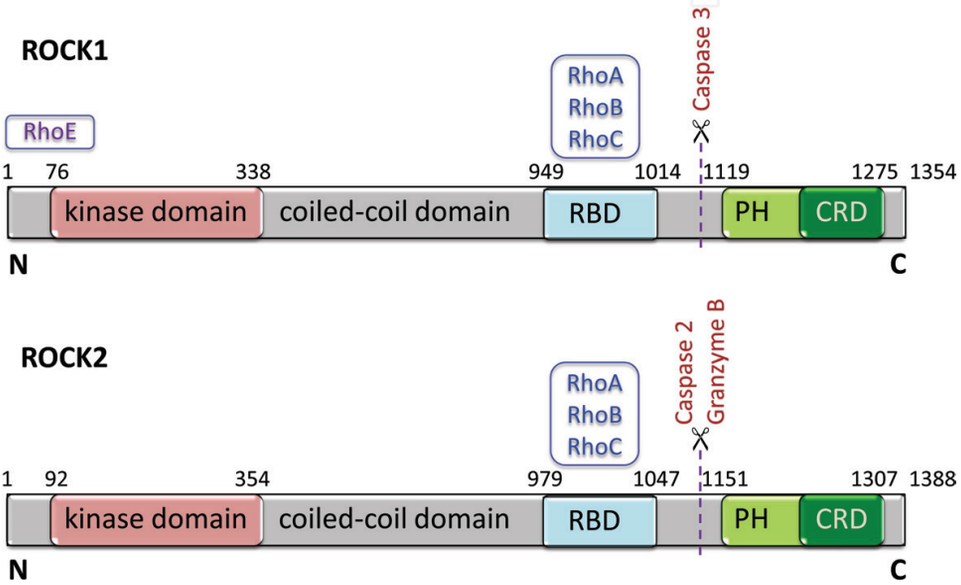


**Figure 1.** Schematic molecular structure and main regulators of ROCKs. ROCK sequences comprise a kinase domain located at the amino terminus of the protein, followed by a coiled-coil region containing the Rho-binding domain (RBD) and a pleckstrin homology (PH) domain with a cysteine-rich domain (CRD).

Although ROCK1 and ROCK2 are ubiquitously expressed, ROCK2 is highly expressed in the brain and the heart, whereas ROCK1 is preferentially expressed in the lung, liver, spleen, kidney, and testis [1, 6]. ROCK signaling has been implicated in a wide range of fundamental cellular functions including cell morphology, contraction, adhesion, motility, migration, proliferation, differentiation, invasion, metastasis, and apoptosis [1, 2]. ROCK can also regulate macrophage phagocytic activity and endothelial cell permeability, and it is known to play a role in inflammatory mechanisms and endothelial dysfunction [7, 8].

## 2. ROCK polymorphisms and disease susceptibility

There are only limited numbers of published studies related to *ROCK* polymorphisms in humans. However, the contribution of the genetic studies related to *ROCK* variants to the disease states is emerging.

### 2.1. Cancer

It has been demonstrated that *ROCK2* gene rs2230774 (Thr431Asn), but not rs1130757 (Arg83Lys), polymorphism is significantly associated with metastases of breast cancer [9]. Although homozygous carriers of the Thr431Thr genotype were more frequent, heterozygous carriers of the Thr431Asn genotype were less frequent among the metastatic patients than among controls. There was also an increase in Thr431 allele and decrease in Asn431 allele frequencies in patients with distant metastases. Furthermore, increased Thr431Thr genotype and Thr431 allele frequencies were found to be associated with negative estrogen and progesterone receptor status in the metastatic group [9]. This data suggest that Thr431Asn polymorphism of the *ROCK2* gene is a risk factor for the metastases of the breast cancer, and may help in predicting the prognosis. Indeed, activating *ROCK1* mutations (Y405*, S1126*, and P1193S) that increase cellular motility through actin cytoskeleton rearrangement have been identified in breast and lung carcinomas [10]. The Y405* and S1126* mutants, which lead to premature termination of translation at Tyr405 and Ser1126, were both identified in primary human breast cancers, whereas the third mutation, P1193S, which leads to a substitution of proline 1193 with serine, was identified from the established human non-small-cell lung carcinoma line NCI-H1770. rs11874761 rs8085504 rs2127958 rs17202375 rs288980 polymorphisms of the *ROCK1* gene were studied in patients with non-small cell lung cancer, but no association was observed [11]. Thus, no evidence was found to suggest that these polymorphisms play a significant role in lung cancer susceptibility [11]. Recently, a nonsense mutation (G285*) in *ROCK1* that introduces a premature stop codon at amino acid 285, and a *ROCK2* mutation (S457N) has been identified in gastric cancer patients with peritoneal carcinomatosis [12]. Collectively, these results may suggest the importance of the ROCK gene in breast, lung, and gastric carcinomas.

There are some controversial results about the association between the *ROCK* polymorphisms and colorectal carcinoma. Significant associations between *ROCK1* (rs73963110 and rs35996865) and *ROCK2* gene polymorphisms (rs2290156, rs10178332, rs35768389, rs10929732 and rs34945852) with colorectal cancer development have been detected [13]. However, no marked associations were found between *ROCK2* gene rs965665, rs2230774, rs6755196, and rs1515219 polymorphisms and the risk of developing colorectal cancer [13]. ROCK and p53 immunohistochemical stainings were found to be markedly elevated in the tumor tissue. There were also significant correlations between vascular and perineural invasions with ROCK2 or p53 protein expressions [13]. These data showed that the *ROCK1* and *ROCK2* genes might be a risk factor for colorectal cancer development, and that genetic polymorphism in these genes may modify individual susceptibility to colorectal cancer in the Turkish population [13]. However, none of the allelic or genotypic variants of the four *ROCK1* (rs35996865, rs73963110, rs2127958, and rs288980) and five *ROCK2* (rs12692437, rs7563468, rs35768389, rs17463896, and rs16857265) polymorphisms was found to be associated with the occurrence of colorectal cancer or with the development of regional lymph node metastasis in an Italian population [14]. It is noteworthy that no evidence of an association was found for *ROCK2* rs35768389 or for *ROCK1* rs73963110 variants, which have been previously described as relevant to colorectal cancer development in a Turkish cohort [13]. On the other hand, Zucchini et al. [14]. found that the *ROCK1* rs35996865 G variant allele was significantly more frequent in male patients than in the control group. This

finding points to a possible gender-related modulation by the *ROCK1* gene in colorectal cancer susceptibility.

Although there were no significant associations between *ROCK2* gene polymorphisms [rs2290156, rs965665, rs10178332, rs2230774 (Thr431Asn), rs2230774 (Thr431Ser), rs6755196, and rs726843] and mantle cell lymphoma cases, ROCK1 protein and gene expressions were markedly increased in lymph node tissues of the patients [15]. Demonstration of no significant associations between *ROCK2* gene polymorphisms and mantle cell lymphoma cases may be due to the differences in pathogenesis between different types of cancer as well as the small number of cases in this study [15].

*ROCK1* gene rs35996865 polymorphism was significantly associated with the increasing risk of clear cell renal cell carcinoma in a Chinese population [16]. However, no significant associations were found with *ROCK1* gene rs8089974 and rs11874761 polymorphisms. Results of this study indicate that the risk of clear cell renal cell carcinoma is increased in participants with G allele of rs35996865.

### 2.2. Cardiovascular diseases

Seasholtz et al. [17] reported that rs2230774 (Thr431Asn) polymorphism at *ROCK2* gene predicts increased blood pressure, systemic vascular resistance, and resistance in response to the endogenous renin-angiotensin system in twins. The Asn/Asn genotype was associated with a greater resting systolic, diastolic, and mean blood pressures. Systemic vascular resistance was found to be higher in Asn/Asn individuals, and aldosterone secretion was lowest in Asn/Asn homozygotes [17]. Rankinen et al. [18] showed that a major haplotype block at the *ROCK2* locus (containing the minor alleles of rs965665, rs10178332, rs6755196, and rs10929732) is recessively associated with a lower risk of hypertension. However, it has been shown that *ROCK2* Thr431Asn polymorphism does not exhibit any significant allele or genotype association with hypertension in a Chinese Han population [19]. Consistently, another Chinese population study did not detect the association between *ROCK2* gene polymorphisms and hypertension [20]. Liu et al. [20] tested the association between coronary artery disease and *ROCK2* gene rs978906, rs2230774 (Thr431Asn), rs56304104 polymorphisms, but no significant association was detected in a Chinese population. This study also does not support a major role for these three *ROCK2* polymorphisms in determining blood pressure levels. Thus, results of this analysis do not support common variants in the coding region of *ROCK2* to have a major effect to coronary artery disease susceptibility.

Significant associations were observed for GG genotype of rs978906, AA genotype of rs6753921, GG genotype of rs10495582, and AA genotype of rs2230774 (Thr431Asn) polymorphisms with high-altitude essential hypertension in Indian high-altitude native Ladakhi population [21]. Haplotype GAGA composed of variant alleles was found to be in higher proportion in cases [21]. Other six polymorphisms (rs2290156, rs10167277, rs10929727, rs6716817, rs4477886, and rs10929728) were also studied, but no marked changes were noted in this study [21]. Associations of *ROCK2* gene polymorphisms with elevated systolic blood pressure levels suggest the involvement of these four polymorphisms in high-altitude essential hypertension.

Peterson et al. [22] evaluated allelic variants [rs12622447, rs10929728, rs1868584, rs6716817, rs2230774 (Thr431Asn), rs5829297, rs4027164, and rs17366517] or haplotypic associations of *ROCK2* in women with preeclempsia in a Finnish population and did not detect any significant association, implying that *ROCK2* gene could not be a functional target for the regulation of preeclempsia. It is concluded that common genetic variations in *ROCK2* are unlikely to make a major contribution to the risk of preeclampsia in the Finnish population. However, *ROCK2* gene intronic rs1868584 variant is reported to be associated with cardiovascular disease and hypertension [23].

The major alleles of rs978906 (A allele) and rs2230774 (C allele) of *ROCK2* gene were found to be significantly associated with arterial stiffness in a Chinese population residing in Taiwan [24]. They found that the A allele of rs978906 has reduced repression of miR-1183 resulting in significantly higher ROCK2 expression levels than the G allele. It has been proposed that people carrying the A allele are prone to arterial stiffness because their ROCK2 levels tend to be high [24]. Thus, these two functional polymorphisms of *ROCK2* gene can increase the susceptibility of arterial stiffness by affecting ROCK2 levels and activity in the Chinese population.

Yoo et al. [25] demonstrated that the genotype frequencies of five polymorphisms (rs978906, rs2271621, rs2230774, rs1515219 and rs3771106) of *ROCK2*, in the vasospastic angina group, were not significantly different from that in the control group in the Korean population. The only marked difference was noted in haplotype analysis [25]. The haplotype GTCTG was significantly associated with a decreased risk of vasospastic angina, suggesting that the *ROCK2* gene might be involved in the pathogenesis of vasospastic angina in the Korean population.

No association of the *ROCK2* gene rs2230774 (Thr431Asn) polymorphism with the development of cardiac septal defects in pediatric patients has been reported [26], suggesting that this polymorphism is not a contributing factor to the susceptibility of atrial or ventricular septal defects.

Palomino Doza et al. [27] investigated the role of genetic variations in *ROCK1* on the risk of tetralogy of Fallot in British Caucasian patients, and found that *ROCK1* gene rs288979 and rs56085230 (Tyr269Tyr) variants were significantly associated with tetralogy of Fallot. In this study, *ROCK1* gene rs2292296 (Leu1097Phe), rs7237677, rs7227454, rs288989, rs45449301 (Ile432Val), rs288979, rs17202368, rs17202375, rs2271255 (Lys222Glu), rs1481280, rs8085504, rs398528, rs112165707 (Ser595Ser), and rs45562542 (Thr773Ser) polymorphisms were also studied, but no significant changes were determined [27].

### 2.3. Autoimmune diseases

Significant differences between systemic sclerosis patients and control group were observed with regard to rs35996865 polymorphism of the *ROCK1* gene and rs10178332 polymorphism of the *ROCK2* gene [28]. CC genotype frequency of the rs35996865 polymorphism was found to be extremely low in patients with Raynaud's phenomenon [28]. A significant difference between systemic sclerosis patients and control group was observed in G allele and GG genotype distributions of alteration in the *ROCK2* gene rs10178332 polymorphism. Additionally, GG allele frequency was significantly low in patients with Raynaud's phenomenon and lung involvement [28]. In this study, rs112108028 (Pro1164Leu) and rs1045144 for *ROCK1*; rs2230774 (Thr431Ser),

rs2230774 (Thr431Asn), rs35768389 (Asp601Val), rs726843, rs2290156, rs965665, rs6755196, and rs10929732 for *ROCK2* gene polymorphisms were also examined, but no marked associations were noted. These results strongly suggest that rs35996865 and rs10178332 polymorphisms may be important risk factors for the development of systemic sclerosis.

It has been reported that *ROCK2* gene rs35768389 (Asp601Val) polymorphism is associated with Behçet's disease [29]. There are marked elevations in both TA genotype and A allele frequencies of this polymorphism in patients group. Although CC genotype of rs1515219 polymorphism was more frequent, CT genotype was less frequent among the patients with Behçet's disease. There was an increase in C allele frequency in patients [29]. Additionally, high AC and TT haplotype frequencies, and an increase in peripheral blood mRNA *ROCK2* gene expression were observed in cases with Behçet's disease. However, no associations were found with rs726843, rs2290156, rs965665, rs10178332, rs2230774, rs6755196, rs10929732, and rs34945852 polymorphisms [29]. These results strongly suggest that *ROCK2* gene polymorphisms may act as a contributing factor to the individual susceptibility of Behçet's disease.

*ROCK1* gene polymorphisms may also have a significant impact on susceptibility to Behçet's disease. In the presence of CC genotype for rs73963110, CT genotype for rs111874856 (Val355Ile), and TC genotype for rs112130712 (Lys1054Arg) polymorphisms, the risk of Behçet's disease increased 12.13-, 15.05-, and 16.28-fold, respectively [30]. A lower frequency of the GA genotype of the rs112108028 (Pro1164Leu) polymorphism was associated with increased risk of Behçet's disease. Moreover, all these polymorphisms showed marked associations with the manifestations of Behçet's disease. Oguz et al. [30] showed that TC and CC genotypes and C allele of the rs73963110 polymorphism, TC genotype and C allele of the rs112130712 polymorphism, CT genotype and T allele of the rs111874856 polymorphism, and GG genotype and G allele of the rs112108028 polymorphism may increase the susceptibility to Behçet's disease. Although CTCG, CCTG, and TCTG haplotype frequencies were high in the patient group, TTCA haplotype frequency was low in Behçet's disease. Interestingly, CCTG and TCTG haplotypes were absent in the control group, while they had 9.5 and 6.8% frequencies in cases with Behçet's disease, respectively [30]. These two haplotypes can be advocated as a biomarker for early prediction of developing Behçet's disease in a Turkish population. However, no marked associations were detected between rs35996865, rs111312709 (Thr792Ala), and rs2271255 (Lys222Glu) polymorphisms and Behçet's disease [30]. Taken together, these data showed that *ROCK* gene appears to be a risk factor for Behçet's disease, and genetic polymorphisms in *ROCK* genes modify individual susceptibility to Behçet's disease. These findings may also provide important insight into the future development or use of potential therapeutic approaches, such as ROCK inhibitors, for patients with Behçet's disease.

There is also evidence that *ROCK2* gene intronic rs1868584 variant was shown to be associated with rheumatoid arthritis [23].

### 2.4. Ocular diseases

There are only two published association studies related to *ROCK* gene polymorphisms in ocular diseases. No evidence for an association of *ROCK2* gene rs2230774 (Thr431Asn)

and rs1130757 (Arg83Lys) polymorphisms with diabetic retinopathy has been reported in a Turkish Population [31]. Additionally, the haplotypes are not significantly associated with diabetic retinopathy as shown in this study [31]. Moreover, another recent study demonstrated that the polymorphisms for the *ROCK1* (rs35996865) and *ROCK2* [rs2290156, rs965665, rs10178332, rs2230774 (Thr431Asn), rs2230774 (Thr431Ser), rs6755196, and rs726843] genes are not associated with the increased risk of development of primary open-angle glaucoma in a Turkish population [32]. There were also no marked associations between the haplotype frequencies and primary open-angle glaucoma. Collectively, these results suggest that studied *ROCK1* and *ROCK2* gene polymorphisms are not contributing factors to the susceptibility of diabetic retinopathy or primary open-angle glaucoma.

### 2.5. Ischemic stroke

In a large prospective study, associations of *ROCK1* gene variants with the risk of ischemic stroke have been observed in healthy Caucasian women [33]. Seven (rs7239317, rs2127958, rs1481280, rs1006881, rs11874761, rs10083915, and rs11873284) of the tagging single nucleotide polymorphisms evaluated in *ROCK1* gene were associated significantly with the risk of ischemic stroke [33]. rs288980 polymorphism was also studied, but no marked association was observed. Thus, *ROCK1* gene variation may influence the risk of ischemic stroke. In contrast, none of the polymorphisms (rs921322, rs8996, rs6753921, rs2230774, rs1515219, rs6716817, rs10203916, rs6755337, and rs12622447) in *ROCK2* were associated with the risk of ischemic stroke [33]. These findings may highlight the potential prognostic utility of *ROCK1*-associated gene variation in the prediction of the risk of ischemic stroke.

### 2.6. Metabolic syndrome

*ROCK1* gene rs35996865 polymorphism and *ROCK2* gene rs2230774 (Thr431Asn) polymorphism are markedly associated with the obesity-related metabolic syndrome in a Turkish population [34]. However, no significant associations with the other 9 *ROCK* polymorphisms [*ROCK1*: rs73963110, rs112108028 (Pro1164Leu), and rs111312709 (Thr792Ala), *ROCK2*: rs2230774 (Thr431Ser), rs726843, rs2290156, rs965665, rs10178332, and rs6755196] have been observed [34]. These results suggest that CA and AA genotypes and A allele of the rs35996865 polymorphism, and CC genotype and C allele of the rs2230774 (Thr431Asn) polymorphism may increase the individual susceptibility to metabolic syndrome.

### 2.7. Respiratory distress syndrome

There is evidence that *ROCK1* gene rs2271255 (Lys222Glu) and rs35996865 polymorphisms, and *ROCK2* gene rs726843, rs2290156, rs10178332, rs35768389 (Asp601Val) polymorphisms are significantly associated with respiratory distress syndrome, and that these polymorphisms could be a risk factor for the development of neonatal respiratory distress syndrome [35]. High odds ratios were observed with these polymorphisms. However, no associations were found with rs73963110, rs1515219, rs965665, rs2230774 (Thr431Asn), rs6755196, and rs10929732 polymorphisms. Additionally, 12 haplotypes (6 in *ROCK1* and 6 in *ROCK2*) were

found to be markedly associated with respiratory distress syndrome. Interestingly, TGCA and TGCT haplotypes were only observed among the cases. Although none of the controls had TGCT haplotype, it was seen in 26% of the infants with respiratory distress syndrome [35]. It should be emphasized that rs2271255 (Lys222Glu) and rs726843 polymorphisms have not been associated with any other disease yet. Collectively, these results strongly suggest that *ROCK* gene polymorphisms may modify individual susceptibility to respiratory distress syndrome in neonates.

### 2.8. Kidney disease

It has been demonstrated that rs2230774 (Thr431Asn) polymorphism of *ROCK2* gene is significantly associated with chronic kidney disease in individuals with a low serum concentration of triglycerides, with the A allele being protective against this condition [36]. Rao et al. [37] showed that rs1515219 and rs2290156 polymorphisms of the *ROCK2* gene are associated with urinary albumin excretion in twin pairs.

### 2.9. Overactive bladder

Gurocak et al. [38] found that genotype and allele frequencies were not significantly different between the children with overactive bladder and the control group for *ROCK2* gene rs2230774 (Thr431Asn) polymorphism. It was concluded that this polymorphism has no impact on the response to anticholinergic treatment.

### 2.10. Epilepsy

Association of the Thr431Asn polymorphism with idiopathic generalized epilepsy has been investigated in a study [39]. Genotype distributions and the allele frequencies for the Thr431Asn polymorphism showed no significant differences between the control and epilepsy groups. Moreover, this polymorphism did not influence age of epilepsy onset, family history, single or combined drug treatments, or status epilepticus [39]. Therefore, these results suggest that the Asn431 *ROCK2* variant allele is not an important risk factor for the development of idiopathic generalized epilepsy and does not influence the main clinical characteristics of idiopathic generalized epilepsy.

### 2.11. Migraine

Uslu Kuzudisli et al. [40] have investigated the association of the Thr431Asn polymorphism with migraine in a Turkish population. No statistically significant association between a migraine and genotype distributions or the allele frequencies for the *ROCK2* gene Thr431Asn polymorphism was demonstrated. In addition, there were no marked differences in genotype and allele frequencies for the migraine without aura and migraine with aura subgroups when compared with control group [40]. These findings suggest that the *ROCK2* gene Thr431Asn polymorphism is not a risk factor for the migraine, and it is not involved in the migraine pathogenesis.

### 2.12. Diabetes

It has been reported that *ROCK2* gene rs2230774 (Thr431Asn) and rs1130757 (Arg83Lys) polymorphisms were not associated with the risk of diabetes (mainly type-2) [31], suggesting that these polymorphisms are not a contributing factor to the susceptibility of diabetes in a Turkish population. However, Ross [23] presented evidence for the association of *ROCK2* rs1868584 variant with type-1 diabetes.

### 2.13. High altitude pulmonary edema

Pandey et al. [41] investigated a total of 13 *ROCK2* gene polymorphisms (rs978906, rs6753921, rs2290156, rs10495582, rs2230774, rs10167277, rs13393192, rs10929727, rs6716817, rs4477886, rs41264193, rs12622447, and rs10929728), but one polymorphism (rs10929728) emerged significant among the study groups. A significant association was observed for C allele of the rs10929728 with high altitude pulmonary edema [41]. Thus, an overrepresentation of *ROCK2* rs10929728C demonstrated the role of this allele in increasing the risk susceptibility to high altitude pulmonary edema. These data may suggest that stress-activated *ROCK2* gene has a role in predisposing an individual to high altitude pulmonary edema.

### 2.14. Psychiatric disorders

*ROCK2* rs1868584 polymorphism was shown to be associated with bipolar disorder [23]. No associations between *ROCK1* gene rs8085654, rs288980, and rs1481280 polymorphism and schizophrenia have been reported in a Japanese population [42]. No correlations were also detected between these *ROCK1* genotypes and Brief Psychiatric Rating Scale scores, amounts of antipsychotics, or age at onset in that study.

**Tables 1** and **2** show the significant and insignificant associations of *ROCK* polymorphisms with disease states.

| Disease | Significant association | Ref. | Insignificant association | Ref. |
|---|---|---|---|---|
| Breast cancer | Y405*, S1126* | [10] | | |
| Lung cancer | P1193S | [10] | rs11874761, rs8085504, rs2127958, rs17202375, rs288980 | [11] |
| Gastric cancer | G285* | [12] | | |
| Colorectal cancer | rs73963110, rs35996865 | [13] | rs35768389, rs73963110, rs2127958, rs288980 | [14] |
| | rs35996865 (in male patients) | [14] | | |
| | V1309* | [43] | | |
| Clear cell renal cell carcinoma | rs35996865 | [16] | rs8089974, rs11874761 | [16] |
| Tetralogy of Fallot | rs288979, rs56085230 (Tyr269Tyr) | [27] | rs2292296 (Leu1097Phe), rs7237677, rs7227454, rs288989, rs45449301 (Ile432Val), rs288979, rs17202368, rs17202375, rs2271255 (Lys222Glu), rs1481280, rs8085504, rs398528, rs112165707 (Ser595Ser), rs45562542 (Thr773Ser) | [27] |

| Disease | Significant association | Ref. | Insignificant association | Ref. |
|---|---|---|---|---|
| Systemic sclerosis | rs35996865 | [28] | rs112108028 (Pro1164Leu), rs1045144 | [28] |
| Behçet's disease | rs73963110, rs111874856 (Val355Ile), rs112130712 (Lys1054Arg), rs112108028 (Pro1164Leu) | [30] | rs35996865, rs111312709 (Thr792Ala), rs2271255 (Lys222Glu) | [30] |
| Primary open-angle glaucoma | | | rs35996865 | [32] |
| Ischemic stroke | rs7239317, rs2127958, rs1481280, rs1006881, rs11874761, rs10083915, rs11873284 | [33] | rs288980 | [33] |
| Obesity-related metabolic syndrome | rs35996865 | [34] | rs73963110, rs112108028 (Pro1164Leu), rs111312709 (Thr792Ala), | [34] |
| Respiratory distress syndrome | rs2271255 (Lys222Glu), rs35996865 | [35] | rs73963110 | [35] |
| Schizophrenia | | | rs8085654, rs288980, rs1481280 | [42] |

**Table 1.** Significant and insignificant associations between *ROCK1* variants and disease susceptibility.

| Disease | Significant association | Ref. | Insignificant association | Ref. |
|---|---|---|---|---|
| Breast cancer | rs2230774 (Thr431Asn) | [9] | rs1130757 (Arg83Lys) | [9] |
| Gastric cancer | S457N | [12] | | |
| Colorectal cancer | rs2290156, rs10178332, rs35768389, rs10929732, rs34945852 | [13] | rs965665, rs2230774, rs6755196, rs1515219 | [13] |
| | | | rs12692437, rs7563468, rs35768389, rs17463896, rs16857265 | [14] |
| Mantle cell lymphoma | | | rs2290156, rs965665, rs10178332, rs2230774 (Thr431Asn), rs2230774 (Thr431Ser), rs6755196, rs726843 | [15] |
| Hypertension | rs2230774 (Thr431Asn) | [17] | rs2230774 (Thr431Asn) | [19] |
| | rs965665, rs10178332, rs6755196, rs10929732 | [18] | rs978906, rs2230774 (Thr431Asn), rs56304104 | [20] |
| | rs1868584 | [23] | | |
| High-altitude essential hypertension | rs978906, rs6753921, rs10495582, rs2230774 (Thr431Asn) | [21] | rs2290156, rs10167277, rs10929727, rs6716817, rs4477886, rs10929728 | [21] |
| Preeclampsia | | | rs12622447, rs10929728, rs1868584, rs6716817, rs2230774 (Thr431Asn), rs5829297, rs4027164, rs17366517 | [22] |
| Arterial stiffness | rs978906, rs2230774 (Thr431Asn) | [24] | | |
| Vasospastic angina | GTCTG haplotype | [25] | rs978906, rs2271621, rs2230774, rs1515219, rs3771106 | [25] |

| Disease | Significant association | Ref. | Insignificant association | Ref. |
|---|---|---|---|---|
| Cardiac septal defects | | | rs2230774 (Thr431Asn) | [26] |
| Systemic sclerosis | rs10178332 | [28] | rs2230774 (Thr431Ser), rs2230774 (Thr431Asn), rs35768389 (Asp601Val), rs726843, rs2290156, rs965665, rs6755196, rs10929732 | [28] |
| Behçet's disease | rs35768389 (Asp601Val), rs1515219 | [29] | rs726843, rs2290156, rs965665, rs10178332, rs2230774, rs6755196, rs10929732, rs34945852 | [29] |
| Rheumatoid arthritis | rs1868584 | [23] | | |
| Diabetic retinopathy | | | rs2230774 (Thr431Asn), rs1130757 (Arg83Lys) | [31] |
| Primary open-angle glaucoma | | | rs2290156, rs965665, rs10178332, rs2230774 (Thr431Asn), rs2230774 (Thr431Ser), rs6755196, rs726843 | [32] |
| Ischemic stroke | | | rs921322, rs8996, rs6753921, rs2230774, rs1515219, rs6716817, rs10203916, rs6755337, rs12622447 | [33] |
| Obesity-related metabolic syndrome | rs2230774 (Thr431Asn) | [34] | rs2230774 (Thr431Ser), rs726843, rs2290156, rs965665, rs10178332, rs6755196 | [34] |
| Respiratory distress syndrome | rs726843, rs2290156, rs10178332, rs35768389 (Asp601Val) | [35] | rs1515219, rs965665, rs2230774 (Thr431Asn), rs6755196, rs10929732 | [35] |
| Chronic kidney disease | rs2230774 (Thr431Asn) | [36] | | |
| Urinary albumin excretion | rs1515219, rs2290156 | [37] | | |
| Overactive bladder | | | rs2230774 (Thr431Asn) | [38] |
| Idiopathic generalized epilepsy | | | rs2230774 (Thr431Asn) | [39] |
| Migraine | | | rs2230774 (Thr431Asn) | [40] |
| Diabetes | rs1868584 (with type-1 diabetes) | [23] | rs2230774 (Thr431Asn), rs1130757 (Arg83Lys) | [31] |
| High altitude pulmonary edema | rs10929728 | [41] | rs978906, rs6753921, rs2290156, rs10495582, rs2230774, rs10167277, rs13393192, rs10929727, rs6716817, rs4477886, rs41264193, rs12622447, rs10929728 | [41] |
| Bipolar disorder | rs1868584 | [23] | | |

**Table 2.** Significant and insignificant associations between *ROCK2* variants and disease susceptibility.

## 3. Structure or function of the ROCK enzymes affected by polymorphisms

The Thr431Asn polymorphism lies immediately carboxyl-terminal to the start of the putative coiled-coil region and encodes an amino acid substitution in the predicted coiled-coil domain of the protein, which is associated with ROCK2/ROCK2 parallel homodimerization

and Rho binding. Asp601Val polymorphism is also located on the coiled-coil region. Because the dimeric structure of ROCK is essential for normal *in vivo* function [4, 5], changes in the coiled-coil region could be hypothesized to effect dimerization, Rho binding, and thereby ROCK activation and phosphorylation of its substrates. Indeed, it has been demonstrated for rs2230774 (Thr431Asn) polymorphism that cells transfected with C allele constructs have significantly higher ROCK activities than those with A allele constructs [24]. Moreover, the average leukocyte ROCK activity was found to be highest in CC genotype, followed by AC and then lowest in AA [24]. Taken together, non-synonymous polymorphism rs2230774 (Thr431Asn) influences ROCK2 activity.

Three *ROCK1* mutations (Y405*, S1126*, and P1193S) attenuate the autoinhibitory domain at the carboxy-terminal end of the protein and enhance kinase activity [10]. In a colorectal cancer study, the *ROCK1* mutation (typically c.3921delA leading to V1309*) is also predicted to partially delete the autoinhibitory domain [43]. *ROCK1* nonsense mutation (G285*) introduces a premature stop codon at the 285th amino acid of ROCK1, leading to the truncation of ~79% of ROCK1 [12]. The lack of a Rho-binding domain by the *ROCK1* mutation could impair the Rho/ROCK pathway [12]. Therefore, this mutation may cause the loss-of-function of ROCK1, because most of the functional domains, including the Rho-binding domain, are truncated by the mutation. The rs56085230 (Tyr269Tyr) variant is synonymous and located within the kinase motif of the protein which might influence splicing [27]. *ROCK2* gene rs978906 polymorphism located at 3′-UTR is predicted to influence microRNA(miR)-1183 binding to ROCK2 [24]. Thus, 3′-UTR rs978906 polymorphism affects the ROCK2 protein synthesis by interfering miR-1183 binding. miR-1183 may modulate the disease states by fine tuning the ROCK2 protein expression.

It has been reported that polymorphism can change the binding of the transcription factors to the gene. Pandey et al. [41] found that the variant allele rs10929728C of the *ROCK2* gene binds to a transcription factor Nkx-2, but the wild-type allele rs10929728T binds to CdxA. Bioinformatic analysis also revealed that serum response factor, a transcription factor, binding site was found for the variant allele G of the *ROCK2* gene rs10495582 polymorphism [21]. Serum response factor is known to promote the transcriptional expression of ROCK2 [44]. In general, the structural or functional changes of the ROCK enzymes affected by polymorphisms are mostly unknown and require further studies.

## 4. Conclusions

There are some inconsistent results with the association studies, which can be explained in part by population stratification, ethnic differences, selection bias, genotyping errors, or other factors. The incomplete polymorphism coverage likely does not represent the entire gene and therefore may not fully describe the contribution of *ROCK* genes. In the future, systematic and large prospective studies or meta-analysis are warranted to evaluate thoroughly the role of *ROCK1* and *ROCK2* genes in the genetic predisposition to disease. The structure or function of the ROCK enzymes affected by polymorphisms is mostly unknown, and functional studies

would be very helpful in elucidating the involvement of ROCK in disease pathogenesis. Further validations from larger, independent cohorts as well as perspective studies are also required to verify presently known associations in different ethnic groups. Furthermore, identification of functional mutations could potentially help in the development of ROCK-specific therapies for ROCK-related disease states.

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