Polymorphism of the Serotonin Transporter Gene and Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

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Background—The serotonin transporter (5-HTT) is involved in the pulmonary artery smooth muscle hyperplasia that leads to pulmonary hypertension (PH). Because hypoxia and 5-HTT gene polymorphism control 5-HTT expression, we examined 5-HTT gene polymorphism and PH in hypoxemic patients with advanced chronic obstructive pulmonary disease (COPD).

Methods and Results—In 103 patients with COPD recruited in France (n=67) and the UK (n=36), we determined 5-HTT gene polymorphism and pulmonary artery pressure (PAP) measured during right heart catheterization (France) or Doppler echocardiography (UK). Ninety-eight subjects from the 2 countries served as control subjects. The distribution of 5-HTT gene polymorphism did not differ between patients and control subjects. In patients carrying the LL genotype, which is associated with higher levels of 5-HTT expression in pulmonary artery smooth muscle cells than the LS and SS genotypes, PH was more severe than in LS or SS patients. Mean PAP values in patients from France with the LL, LS, and SS genotypes were 34±3, 23±1, and 22±2 mm Hg (mean±SEM), respectively (P<0.01). Corresponding systolic PAP values in the UK were 40±3, 28±3, and 24±3 mm Hg, respectively (P<0.01). Compared with control subjects, platelet 5-HTT protein was increased in COPD patients in proportion to the hypoxemia level, and strong 5-HTT immunostaining was observed in remodeled pulmonary arteries from COPD patients.

Conclusions—5-HTT gene polymorphism appears to determine the severity of PH in hypoxemic patients with COPD. Because PH is an important prognostic factor in this disease, recognition of patients at risk for PH should be helpful in managing COPD. (Circulation. 2003;108:1839-1844.)

Key Words: chronic pulmonary disease ■ pulmonary hypertension ■ genes

Chronic obstructive pulmonary disease (COPD) is the most common cause of pulmonary hypertension (PH) and cor pulmonale.1 Although PH is usually mild to moderate in COPD, it is associated with a poor prognosis.2,3 Long-term oxygen therapy improves the prognosis of patients with COPD and stabilizes pulmonary artery pressure (PAP).4,5 However, even in patients receiving long-term oxygen therapy, PH is the strongest prognostic factor, independent of the severity of airflow limitation or hypoxemia.3,6

The pathogenesis of PH in patients with advanced COPD is still incompletely understood. Chronic hypoxia is considered the major contributing factor, in association with morphological changes in lung parenchyma and inflammation.7,8 However, PAP values vary greatly among individuals with COPD, with some patients developing severe PH out of proportion with the severity of their underlying disease.9,10 Recognition of a genetic susceptibility to PH in COPD patients would have important implications for a clear understanding of the pathogenesis and potentially the treatment or prevention of PH, which might improve the prognosis.

Recent years have witnessed the identification of biological processes pivotal to the complex vascular changes associated with various forms of PH. We recently reported that serotonin (5-hydroxytryptamine, 5-HT) and its transporter (5-HTT) play a critical role in the pulmonary vascular smooth muscle hyperplasia and vascular remodeling associated with experimental hypoxic PH and human primary PH.11,12 The 5-HTT overexpression seen in pulmonary vessels of patients with primary PH is at least partly related to an insertion/deletion polymorphism in the promoter region of the 5-HTT gene12 with long (L) and short (S) forms: the L allele drives a 2- to 3-fold higher rate of 5-HTT gene transcription than the
S allele. Conversely, hypoxia is a strong inducer of 5-HTT gene expression. We therefore hypothesized that 5-HTT gene polymorphism, in combination with hypoxia, may determine the extent of pulmonary vascular remodeling and, consequently, the severity of PH in patients with advanced hypoxemic COPD.

Methods

Study Population
The study population comprised 103 unrelated patients with COPD and 98 normal subjects. Sixty-seven patients were investigated for moderate to severe COPD in 2 French centers, Strasbourg (n=41) and Nantes (n=26), and 36 patients were admitted to Addenbrooke’s Hospital in Cambridge, United Kingdom. The diagnosis of COPD was based on a history of chronic bronchitis and on evidence of chronic airflow limitation with a forced expiratory volume in 1 second (FEV1)/vital capacity (VC) ratio of <70% and an FEV1 <80% of predicted. The patients were stable and had experienced no acute exacerbations within the previous 6 weeks. Patients with left heart disease, idiopathic pulmonary fibrosis, pulmonary vascular disease, or other chronic pulmonary disease were excluded. All patients were on chronic bronchodilator therapy, and 14 patients were on long-term oxygen therapy. All medications were stopped 24 hours before the study. Right heart catheterization was performed at rest with the patient supine. Right atrial, pulmonary artery (systolic, diastolic, and mean), and pulmonary wedge pressures were measured. Cardiac output was determined by thermodilution. Derived hemodynamic variables were calculated by use of standard formulas: cardiac index (CI, in L·min⁻¹·m⁻²), cardiac output/body surface area, and pulmonary vascular resistance (PVR, in IU/L·m²·min⁻¹) = mean PAP - pulmonary wedge pressure/CI. The 36 patients investigated in Cambridge underwent noninvasive estimation of pulmonary systolic pressure by Doppler echocardiography. Maximal velocity of the tricuspid regurgitant jet was assessed by continuous-wave Doppler from the apical 4-chamber view. Systolic PAP was calculated as 4v² – 5, where v is the peak velocity of the tricuspid regurgitant flow curve. Arterial blood gases and hemoglobin oxygen saturation were measured with an ABL 30 or an OS3M hemoximeter (Radiometer).

All the control subjects (controls) were healthy, and none were known to have acute or chronic illness, except for mild systemic hypertension (21 controls). Before study inclusion, all patients and controls signed an informed consent document, and our institutional review board approved the study.

All subjects underwent blood sampling for 5-HTT genotype determination. Platelet 5-HTT binding activity was investigated in a subgroup of 20 controls and 20 patients whose characteristics were similar to those of the overall study population.

Laboratory Investigations

Genotyping
Genomic DNA was extracted from whole blood and pulmonary artery smooth muscle cells (PA-SMCs) by use of the Mini Genomic Kit (Eurbio). The 5-HTT gene promoter region was amplified by polymerase chain reaction with the oligonucleotide primers 5' -GGGTTGGCCGCTCTGAATGC-3' and 5'-GAGGGACTGAGCTGGACAACCAC-3' with 50 ng of genomic DNA, as previously described. Amplification products were separated by electrophoresis in 2% agarose gel stained with ethidium bromide. The 484- and 528-bp fragments corresponded to the S and L allele variants, respectively.

Measurement of Platelet [3H]Citalopram Binding
Platelets were prepared by platelet-rich-plasma centrifugation as described previously. Specific [3H]citalopram binding was calculated by subtracting nonspecific binding in the presence of 10 mmol/L fluoxetine from total binding and was expressed as fmol [3H]citalopram bound/10⁸ platelets.

Studies on Lungs and PA-SMCs
Lung specimens were obtained during lobectomy or pneumonectomy for localized lung cancer in 18 individuals. Pulmonary arteries were studied at a distance from tumor areas. PA-SMCs were cultured from explants, as described previously, and used between passages 1 and 3. In 4 of these patients, who had COPD as defined above, lung specimens were taken for immunohistochemical analysis.

Quantitative Determination of 5-HTT mRNA
To examine the effect of hypoxia on 5-HTT mRNA expression, cells from carriers of the LL, LS, and SS variants were exposed to hypoxia (5% CO₂, 95% N₂) or normoxia (5% CO₂, 20% O₂, 75% N₂) for 2 hours, washed with PBS, and lysed with guanidine isothiocyanate (Interchim). Total RNA was extracted as described by Chomczynski and Sacchi. Then, competitive reverse transcriptase–polymerase chain reaction was performed on total RNA as previously described.

Lung Immunohistochemical Analysis
Paraffin sections (5 mm thick) of lung specimens were mounted on Superfrost Plus slides (Fisher Scientific) and exposed to goat polyclonal anti–5-HTT antibodies (Santa Cruz Biotechnology) and biotin-labeled anti-goat secondary antibodies (Dako) diluted 1:200 in the same buffer. The sections were then stained with hematoxylin and eosin.

Statistical Analyses
All data are reported as mean±SD, unless specified otherwise. When between-group comparisons using the Kruskal-Wallis test showed significant differences, the groups were compared by a Mann-Whitney U test. Univariate regression analysis was performed between mean PAP and systolic PAP on the one hand and lung function test and arterial blood gas variables on the other hand by the Spearman method. Adjusted odds ratios for moderate to severe PH, defined as systolic PAP ≥40 mm Hg, were calculated by the Mantel-Haenszel method. Allele and genotype frequencies were compared by χ² tests, and the test for Hardy-Weinberg equilibrium was performed in each group. Probability values of P<0.05 were considered statistically significant.

Results

The clinical and respiratory function characteristics of the populations from France and the UK are shown in Tables 1 and 2. All the patients were smokers. Smoking histories and airflow limitation were similar. Arterial oxygen saturation (SaO₂) was slightly lower in the patients from France than from the UK, 91±3% versus 94±3%, respectively (P<0.05). To characterize 5-HTT expression in patients with COPD, we first assessed platelet [3H]citalopram binding in 20 patients with COPD and 20 controls in France. Compared with controls, [3H]citalopram binding to 5-HTT protein within platelets was higher in patients with COPD (Figure 1, P<0.01) and was negatively correlated with SaO₂ (r = −0.44, P<0.05).

The 103 patients with COPD and the 98 controls were similar with regard to sex distribution, age, race, and ethnic group. The distributions of 5-HTT genotypes in patients and controls in the populations from France and the UK were in Hardy-Weinberg equilibrium. Percentages of the LL, LS, and SS genotypes were similar in patients with COPD and in controls in both countries (Table 3). The distribution of patients with COPD by genotype (LL, LS, or SS) is shown in Tables 1 and 2 and Figures 2 and 3. Compared with carriers of LS or SS, LL patients had higher mean or systolic PAP values (Tables 1 and 2, Figures 2 and 3). Pulmonary vascular resistance, which was collected only...
in France, was twice as high in the LL group as in the LS and SS groups (Table 1). Gas exchange parameters and age were similar in the LL, LS, and SS groups. LL patients in France had less severe airway obstruction, with a higher FEV₁ (expressed as % predicted value) and a tendency toward a higher FEV₁/FVC ratio, than did LS or SS patients (Table 1). Pulmonary hemodynamic parameters were similar in the LS and SS groups. Platelet studies performed in the subgroups of 20 patients and 20 controls showed no difference between LL, LS, and SS subjects with respect to [³H]citalopram binding (Figure 1).

Among physiological parameters, only PaO₂ and SaO₂ were correlated with mean PAP, systolic PAP, and PVR. For adjusted odds ratio estimation, the SS and LS groups were combined. To adjust for confounding by hypoxemia, patients were stratified according to the severity of hypoxemia, with an SaO₂ cutoff of 92.5% (median value). The adjusted odds ratio for PH according to 5-HTT gene polymorphism was 4.16 (95% CI, 1.54 to 11.21; \( P = 0.005 \)).

Under normoxic conditions, 5-HTT mRNA levels were almost twice as high in cells homozymous for the L variant as in cells having 1 or 2 copies of the S variant (Figure 4). In addition, LS cells expressed more 5-HTT mRNA than did SS cells. Exposure to hypoxia led to a 2-fold increase in 5-HTT mRNA in each of the cell subgroups, indicating that the effect of hypoxia on 5-HTT expression was additive to that of the polymorphism.

Immunohistochemical examination of lung specimens from controls showed preferential localization of 5-HTT in the media of pulmonary arteries and weaker staining in the endothelium. In comparison, 5-HTT–like immunoreactivity was stronger in lung specimens from patients with COPD.

### Table 1. Clinical Characteristics of French Patients With COPD

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>LL</th>
<th>LS</th>
<th>SS</th>
<th>LL vs LS</th>
<th>LL vs SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>67</td>
<td>21</td>
<td>34</td>
<td>12</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>62±9</td>
<td>64±8</td>
<td>62±9</td>
<td>60±8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>9/58</td>
<td>5/16</td>
<td>2/32</td>
<td>2/10</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco, pack-years</td>
<td>48±18</td>
<td>42±20</td>
<td>52±15</td>
<td>46±22</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.04±0.40</td>
<td>1.21±0.46</td>
<td>0.98±0.37</td>
<td>0.89±0.26</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>37±15</td>
<td>45±16</td>
<td>34±15</td>
<td>31±9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VC, L</td>
<td>2.2±0.7</td>
<td>2.4±0.8</td>
<td>2.2±0.6</td>
<td>2.1±0.6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>47±14</td>
<td>52±15</td>
<td>46±14</td>
<td>42±9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PVR, IU</td>
<td>5.9±4.2</td>
<td>10.2±6.2</td>
<td>4.6±1.7</td>
<td>4.2±2.3</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
| Values are mean±SD. No significant difference was observed between LS and SS patients. SAP indicates systemic artery pressure.

### Table 2. Clinical Characteristics of English Patients With COPD

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>LL</th>
<th>LS</th>
<th>SS</th>
<th>LL vs LS</th>
<th>LL vs SS</th>
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</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>36</td>
<td>11</td>
<td>20</td>
<td>5</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>68±8</td>
<td>68±5</td>
<td>67±10</td>
<td>70±7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>19/17</td>
<td>6/5</td>
<td>10/10</td>
<td>3/2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco, pack-years</td>
<td>54±22</td>
<td>61±17</td>
<td>50±25</td>
<td>60±25</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.01±0.51</td>
<td>0.86±0.42</td>
<td>1.16±0.53</td>
<td>0.76±0.41</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>42±17</td>
<td>38±13</td>
<td>47±18</td>
<td>28±15</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>VC, L</td>
<td>2.5±1.0</td>
<td>2.4±1.1</td>
<td>2.6±0.9</td>
<td>2.5±1.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁/VC, %</td>
<td>41±15</td>
<td>38±13</td>
<td>45±15</td>
<td>32±15</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>95±3</td>
<td>94±3</td>
<td>96±2</td>
<td>90±5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic PAP, mm Hg</td>
<td>32±10</td>
<td>40±11</td>
<td>28±8</td>
<td>25±6</td>
<td>&lt;0.02</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
| Values are mean±SD. No significant difference was observed between LS and SS patients.
especially in the medial layer of pulmonary arteries with marked muscular hypertrophy (Figure 5).

**Discussion**

The severity of PH in patients with COPD appears to be directly related to 5-HTT gene polymorphism, as shown by the markedly higher PAP values in patients carrying the LL genotype than in those carrying the LS and SS genotypes. This suggests that the LL genotype may confer a predisposition to the development of PH during COPD progression independently of the severity of the underlying disease.

The serotonin transporter 5-HTT is encoded by a single gene expressed in several cell types, including neurons, platelets, pulmonary vascular endothelial cells, and PA-SMCs. In previous experimental and human studies, we showed that 5-HTT in SMCs was a key determinant of pulmonary vessel remodeling. In addition to contributing to the uptake and subsequent inactivation of 5-HT passing through the lung, 5-HTT mediates PA-SMC proliferation through its ability to induce internalization of indoleam-

**TABLE 3. Allele Distribution of the 5-HTT Gene Promoter Polymorphism in Patients With COPD and Controls**

<table>
<thead>
<tr>
<th>Study population</th>
<th>LL</th>
<th>LS</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects (n=98)</td>
<td>28 (29)</td>
<td>50 (51)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Patients with COPD (n=103)</td>
<td>32 (31)</td>
<td>54 (52)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects (n=48)</td>
<td>13 (27)</td>
<td>24 (50)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Patients with COPD (n=67)</td>
<td>21 (31)</td>
<td>34 (51)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects (n=50)</td>
<td>15 (30)</td>
<td>26 (52)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Patients with COPD (n=36)</td>
<td>11 (30)</td>
<td>20 (56)</td>
<td>5 (14)</td>
</tr>
</tbody>
</table>

*Values are given as number (percent) of patients. S indicates short variant, and L, long variant of 5-HTT gene polymorphism.*
promoter region of the human 5-HTT gene. The ability of 5-HTT to cause PA-SMC proliferation is directly related to the level of 5-HTT gene expression, which is controlled by environmental and genetic factors. Hypoxia is a strong inducer of 5-HTT expression in vitro and in vivo. The level of 5-HTT expression is also determined genetically via an insertion/deletion polymorphism in the promoter region of the human 5-HTT gene. In the present study, we found that cells from LL subjects expressed 2-fold more 5-HTT mRNA than did cells from SS subjects and that LS subjects had an intermediate level of expression. Because hypoxia per se increased 5-HTT expression 2-fold, 5-HTT expression was increased 5-fold in hypoxic LL cells compared with normoxic SS cells.

We studied 103 COPD patients with moderate to severe hypoxemia and appropriate controls from 2 European populations. The severity of PH varied greatly among the patients and was weakly but significantly correlated with the degree of hypoxemia, in keeping with previous studies. Conversely, no correlation was observed between FEV₁ and PAP. The LL, LS, and SS genotypes occurred with similar rates in COPD patients and controls, indicating that there was no relationship between 5-HTT gene polymorphism and COPD. However, platelet 5-HTT binding activity measured in 20 patients and 20 controls was markedly higher in patients than controls, although the distribution of 5-HTT gene polymorphism was similar in the 2 groups. Because 5-HTT gene polymorphism is known to have no effect on platelet 5-HTT binding activity, and given the inverse correlation between SaO₂ and platelet 5-HTT binding activity, this difference is probably ascribable to the hypoxia associated with COPD.

Our main finding is that the severity of PH in patients with COPD was closely related to polymorphism of the 5-HTT gene promoter. The relationship between PAP and the 5-HTT genotype was observed in the United Kingdom and in France, although different techniques were used to measure PAP in these 2 countries. Mean or systolic PAP was >10 mm Hg higher, and PVR twice as high, in LL patients than LS or SS patients. No significant differences in PAP or PVR were found between LS and SS individuals, in keeping with previous evidence that the S variant may exert a dominant influence. Thus, the present results strongly suggest that L-variant homozygosity may confer susceptibility to PH development in patients with advanced COPD. Another possibility is that the LL genotype may merely be a marker for PH in these patients. This possibility, however, appears unlikely, because we previously found that the LL genotype in cultured human PA-SMCs was associated with an increased growth response to 5-HT and serotonin.

PH is usually defined as a mean PAP >25 mm Hg. However, in patients with PH not related to lung disease, symptoms usually appear when mean PAP is between 30 and 40 mm Hg at rest. Moreover, several reports have suggested that a mean PAP >29 mm Hg may be associated with significantly shorter survival of patients with COPD. It is noteworthy that in our study, such high levels of PAP were observed only in LL patients. Therefore, the presence of the LL genotype should identify patients at risk for developing severe PH during progression of COPD. Given that the LL genotype is present in ~30% of Caucasians, ≥30% of patients with COPD may be at risk for developing severe PH.

The association between the LL genotype and PH prompted us to compare the LL, LS, and SS groups with regard to variables potentially related to PH development. We found no differences with regard to blood gas variables or smoking history. Surprisingly, airflow limitation in patients in France was more severe in SS or LS patients than in LL patients. Although we can only speculate about this observation, it may be suggested that patients with severe PH become symptomatic earlier in the course of their disease, at a stage when they have less airflow limitation than do LS or SS patients. Because the severity of COPD is determined primarily by the FEV₁ value, this unexplained difference also indicates that PH in COPD develops independently of the severity of the underlying lung disease. Given the prognostic
impact of PH, this suggests that early identification of patients with COPD at risk for developing PH might improve the management of the disease by prompting measures targeting PH progression.

Our finding that 5-HTT gene polymorphism may determine PH has important pathogenic implications. PH in COPD patients is usually ascribed to functional consequences of chronic hypoxemia, structural lung parenchyma changes, and inflammation. Although hypoxemia causes pulmonary vasoconstriction, no relationship has been demonstrated between the severity of hypoxic pulmonary vasoconstriction and PAP levels in COPD. Moreover, supplemental oxygen therapy stabilizes but does not reverse PH. Our results linking 5-HTT gene polymorphism to PH point to pulmonary smooth muscle hyperplasia as a major contributing factor in the development of PH in COPD. This is in accordance with pathological studies showing extensive remodeling of pulmonary arterial walls and prominent intimal changes of pulmonary vessels in patients with COPD. Interestingly, we found that 5-HTT–like immunoreactivity predominated in the media of thickened pulmonary arteries in lung specimens from patients with COPD, in keeping with results in experimental hypoxic PH. Protection against hypoxic PH development was found in 5-HTT–deficient mice. These indicate that 5-HTT overexpression in pulmonary vessels plays a key role in the pathogenesis of PH in COPD.

We recently reported that selective 5-HTT inhibitors, such as fluoxetine and paroxetine, inhibited the in vitro proliferative response of SMCs to 5-HT. When given orally to experimental animals exposed to chronic hypoxia, these drugs attenuated the development of pulmonary vascular remodeling. Whether 5-HTT inhibitors might be useful for reducing PH in selected patients with COPD deserves investigation.

The possibility that the gene encoding 5-HTT may be involved in PH was initially considered because 5-HTT is a target for appetite suppressants known to increase the risk of primary PH in humans. In studies of lung tissue and pulmonary arteries from patients with primary PH who underwent lung transplantation, we found increased 5-HTT expression and marked enhancement of the growth response of cultured PA-SMCs to 5-HT but not to other growth factors. 5-HTT inhibitors markedly reduced the growth-stimulating effects of serum and 5-HT, abolishing the difference in PA-SMC growth between patients and controls. Furthermore, the LL genotype was considerably more frequent in patients with primary PH than in controls, implying that this genotype conferred susceptibility to primary PH. The present evidence that 5-HTT gene polymorphism may determine the severity of PH in patients with COPD is consistent with these findings and extends the concept to a much more common pattern of PH. This suggests that the associations linking 5-HTT overexpression and 5-HTT gene polymorphism to susceptibility to PH may exist in several patterns of PH and that 5-HTT inhibition may hold therapeutic potential in human PH.

Acknowledgments

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References

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