Acute intermittent porphyria: comorbidity and shared familial risks with schizophrenia and bipolar disorder in Sweden

Martin Cederlöf, Sarah E. Bergen, Henrik Larsson, Mikael Landén and Paul Lichtenstein

Summary
Acute intermittent porphyria (AIP) has been associated with schizophrenia in some studies, but prior research is limited by the absence of comparison populations. Here, we linked Swedish registers to examine the risk of schizophrenia and bipolar disorder in 717 individuals diagnosed with AIP and their first-degree relatives, compared with matched individuals without AIP and their first-degree relatives. Individuals with AIP had a fourfold increased risk of schizophrenia or bipolar disorder. Similarly, relatives of individuals with AIP had double the risk of schizophrenia or bipolar disorder, suggesting that these associations may be as a result of common genetic influences.

Declaration of interest
None.

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Acute intermittent porphyria (AIP) is an autosomal dominant inherited error of metabolism resulting from a partial deficiency in haem biosynthetic enzymes, caused by mutations in the PBGD gene. The prevalence is approximately 1–2 in 10,000, but the regional variability is considerable and so is the penetrance: in the most frequent AIP mutation in Sweden, the penetrance has been reported to be as low as 40%, but for other rare mutations, 75% of mutation carriers do not develop the disorder. Clinical manifestations of AIP are broad and include neurovisceral crises, neuropathy and a range of psychiatric symptoms. In 1939, Waldenström noted that schizophrenia was common in families with AIP, but no statistical support was provided. Another study detected that 5 out of 40 AIP probands had hallucinations, suggesting a possible association between psychosis and AIP. Interestingly, the PBGD Msp I 2.2 kb allele was subsequently associated with schizophrenia, but later studies failed to replicate this finding. Thus, the link between AIP and schizophrenia remains uncertain, and prior research is limited by the absence of comparison populations. We estimated the risk of schizophrenia in individuals with manifest AIP using Swedish national registers. We then assessed the possible shared familial risks by estimating the risk of schizophrenia in first-degree relatives of individuals with AIP, including both latent AIP gene carriers and relatives without AIP mutations. Bipolar disorder was also included, due to its genetic overlap with schizophrenia.

Method
We conducted a cohort study based on Swedish nationwide registers. The Total Population Register contains demographic data on individuals registered as inhabitants since 1968. The Multi-Generation Register includes individuals born in Sweden since 1932 and individuals living in Sweden since 1960. The Swedish Patient Register contains discharge diagnoses for in- and out-patient psychiatric treatment since 1973 and 2001 respectively. The regional ethical review board in Stockholm approved the study.

Individuals with manifest AIP (exposure) and individuals with diagnoses of schizophrenia and bipolar disorder (outcomes) were identified through their first diagnoses of the respective disorder in the Swedish Patient Register. AIP was defined as a phenotypic diagnosis of the disorder according to ICD-9: 277B and ICD-10: E802A. By this definition, 717 individuals were identified and linked to 2449 of their first-degree relatives. Schizophrenia was defined as at least one in-patient episode of the disorder (ICD-8: 295.0–6, 8–9; ICD-9: 295, A–G, W–X; ICD-10: F20). We used this definition because in-patient schizophrenia diagnoses have high agreement when compared with research diagnoses. Bipolar disorder was defined according to a validated algorithm with 92% agreement when compared with diagnoses based on medical records.

For each individual with AIP and their first-degree relatives, 100 randomly selected individuals matched on gender and birth year were assigned. These individuals were alive, living in Sweden and without any AIP diagnoses at the time of the first diagnosis of the respective index person with AIP they were matched to. Defined this way, we identified 71698 unexposed individuals and 243965 of their first-degree relatives.

To assess risks of schizophrenia and bipolar disorder in individuals with manifest AIP (and their relatives), we compared with individuals without manifest AIP (and their relatives), we estimated risk ratios (RRs) and 95% confidence intervals using conditional logistic regressions. Because shared familial risks, including genetic and environmental factors, are indicated when relatives of individuals with AIP have schizophrenia or bipolar disorder but not manifest AIP, we specified the analyses according to these conditions.

Results
Compared with individuals without manifest AIP, individuals with AIP had fourfold increased risks of being diagnosed with schizophrenia (RR = 3.6, 95% CI 2.0–6.4) or bipolar disorder (RR = 3.7, 95% CI 2.1–6.7). First-degree relatives of individuals with AIP had double the risk of schizophrenia (RR = 1.6, 95% CI 1.0–2.7) and bipolar disorder (RR = 1.8, 95% CI 1.0–3.2, online Table DSI).

Discussion
We observed that individuals with manifest AIP had a fourfold excess risk of being diagnosed with schizophrenia or bipol
disorder. Furthermore, first-degree relatives of individuals with AIP had double the risk of both schizophrenia and bipolar disorder. In addition, there seemed to be an overrepresentation of women among those who had both AIP and bipolar disorder, but the small number of observations did not allow formal testing of this potentially important finding. Our findings are consistent with prior reports of an association between AIP and psychiatric disorders. In the recent investigation based on Swedish data, 16% of individuals with manifest AIP and 7% of latent AIP had double the risk of both schizophrenia and bipolar disorder. Furthermore, first-degree relatives of individuals with AIP, without manifest AIP themselves, also were at increased risk of being diagnosed with schizophrenia or bipolar disorder. This further supports the idea of a shared genetic aetiology. AIP can be seen as a natural model of psychotic and affective illness, as the signs and symptoms in many respects are similar to schizophrenia and bipolar disorder. In AIP, there is a decreased function of tryptophan 2,3-dioxygenase (TDO2) and indoleamine 2,3-dioxygenase (IDO) that forms the first and rate-limiting enzymatic step in kynurenine generation. Intriguingly, the kynurenine pathway has been implicated in both schizophrenia and bipolar disorder. Altered kynurenine metabolism – although associated with many diseases – could thus be one mechanism behind the observed associations. Another possible underlying mechanism is pleiotropic effects of the PBGD gene.

To our knowledge, this is the first study to explore the association between AIP and bipolar disorder and the largest to date to test the association between AIP and schizophrenia. Also, the matched study design used here rules out possible cohort effects. A few important limitations should, however, be considered: part of the observed associations might be as a result of ascertainment bias if AIP modifies a psychiatric disorder in ways that make patients more likely to receive healthcare (for example by worsening symptoms), but the small number of observations did not allow formal testing of this possibility. Finally, despite our large sample size, the limited precision of the estimates warrants some caution. In sum, we found strong associations among relatives of individuals with AIP who themselves did not have a diagnosis of AIP, suggests that this possible concern probably has not severely biased the estimates. Finally, despite our large sample size, the limited precision of the estimates warrants some caution. In sum, we found strong associations between AIP and schizophrenia and bipolar disorder that merit further attention in research and clinical practice.

Funding

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### Table DS1

<table>
<thead>
<tr>
<th>Sample</th>
<th>Schizophrenia</th>
<th>Bipolar disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individuals with AIP</strong></td>
<td>Yes, n (%)</td>
<td>No, n (%) Risk ratio (95% CI)</td>
</tr>
<tr>
<td>Total, n</td>
<td>Yes, n (%)</td>
<td>No, n (%)</td>
</tr>
<tr>
<td>717</td>
<td>705 (98.3)</td>
<td>3.6 (2.0–6.4)</td>
</tr>
<tr>
<td>Individuals with AIP</td>
<td>717</td>
<td>705 (98.3)</td>
</tr>
<tr>
<td>Relatives of individuals with AIP</td>
<td>2449</td>
<td>2435 (99.4)</td>
</tr>
</tbody>
</table>

| **Individuals without AIP**| Yes, n (%)    | No, n (%) Risk ratio (95% CI) |
| Total, n                | Yes, n (%)    | No, n (%)        | Yes, n (%)    | No, n (%)        |
| 718                     | 715 (99.5)    | 3.2 (2.4–4.0)    | 718           | 715 (99.5)    | 3.2 (2.4–4.0)    |
| Individuals without AIP | 718           | 715 (99.5)    | 3.2 (2.4–4.0)    | 718           | 715 (99.5)    | 3.2 (2.4–4.0)    |
| Relatives of individuals without AIP | 2435 | 2431 (99.6) | 1.8 (1.0–3.2) | 2435 | 2431 (99.6) | 1.8 (1.0–3.2) |

Sample: Total number of individuals with acute intermittent porphyria (AIP) and their first-degree relatives, compared with individuals without AIP and their first-degree relatives.
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Supplementary Material
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