Association between *ATG16L1* gene polymorphism and the risk of Crohn’s disease

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Abstract

**Objective:** To perform a meta-analysis to evaluate studies investigating the association between *ATG16L1* gene polymorphism and Crohn’s disease.

**Methods:** PubMed, Embase and Web of Science databases were searched for all studies focusing on the association of *ATG16L1* and Crohn’s disease. Combined odds ratios with 95% confidence intervals were calculated for four genetic models (allelic model: G allele versus A allele; additive model: GG versus AA; dominant model: GA+GG versus AA; recessive model: GG versus GA+AA) using either a random effects or fixed effects model.

**Results:** A total of 47 case–control studies involving 18,638 cases and 30,181 controls were included in the final meta-analysis. There was a significant association between *ATG16L1* and Crohn’s disease for all four genetic models. Significant associations were also shown in subgroup analyses when stratified by study design (population- or hospital-based).

**Conclusion:** In this meta-analysis, the *ATG16L1* genotype was significantly associated with the risk of developing Crohn’s disease.

**Keywords**

*ATG16L1*, autophagy, Crohn’s disease, meta-analysis

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Introduction

Crohn’s disease is a type of inflammatory bowel disease associated with chronic relapsing inflammation of the digestive tract anywhere from the mouth to the anus.¹ Although its aetiopathogenesis remains unclear, it is well established that Crohn’s disease is a complex disorder resulting from

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the interactions of genetic, environmental and microbial factors. Among these, genetic factors may be responsible for a major component of disease susceptibility.²

The role of autophagy processes in the development of inflammatory bowel disease is attracting increasing attention.³ It is possible that genes involved in the autophagy pathway may contribute to the pathogenesis of Crohn’s disease. The autophagy-related 16-like 1 (ATG16L1) gene encodes an important protein involved in the formation of autophagosomes during autophagy.⁴ Genome-wide association studies have shown an association between ATG16L1 polymorphism involving an amino acid change at position 300 and increased susceptibility to Crohn’s disease.⁵,⁶ This substitution of threonine with alanine is the result of a single nucleotide polymorphism in which adenine (A) is replaced with guanine (G). This association has been examined in numerous studies, but the results have been inconsistent. The present meta-analysis was designed to evaluate the association between ATG16L1 and Crohn’s disease using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria.⁷

Materials and methods

Literature search

Two investigators (B.B.Z and B.Y.) systematically searched the databases PubMed (up to June 2016), Embase (1966 to June 2016) and Web of Science (2003 to June 2016), and also references from articles, reviews and abstracts presented at meetings of related scientific societies. The following search terms were used: (“ATG16L1”) AND (“Crohn’s disease” OR “inflammatory bowel diseases”) AND (“polymorphism” OR “mutation” OR “variant” OR “genotype”). Studies were limited to those published in English.

Inclusion criteria and quality assessment

The same two investigators independently screened each of the titles, abstracts and full texts to determine whether the studies met the following criteria: (i) evaluation of the association of Crohn’s disease and ATG16L1 polymorphism; (ii) case–control design; (iii) sufficient data for the estimation of odds ratios (ORs) and 95% confidence intervals (CIs). In addition, a quality assessment was performed on all included studies using the Newcastle–Ottawa Scale (NOS) as described elsewhere.⁸

Data extraction

The following data were collected from each study included in the meta-analysis: first author’s name, publication date, country, total numbers of cases and controls, and frequency of ATG16L1 genotypes in cases and controls.

Statistical analyses

Strength of agreement between the investigators regarding study selection was evaluated using the Kappa statistic. The combined ORs and 95% CIs were calculated for the allelic model (G allele versus A allele), the additive model (GG versus AA), the dominant model (GA + GG versus AA) and the recessive model (GG versus GA + AA) using either the random effects model⁹ or the fixed effects model.¹⁰ Galbraith plots were created to graphically assess the source of any heterogeneity. Publication bias was analyzed using Begg’s funnel plots and Egger’s test, with a P-value < 0.05 being considered representative of statistically significant publication bias.¹¹ Conformity with the Hardy–Weinberg equilibrium amongst the controls was determined using the χ²-square test and was considered to be in agreement when the P-value is ≥ 0.05. All statistical analyses
were performed using Stata statistical software version 11.0 (StataCorp, College Station, TX, USA).

Results

Study characteristics
A total of 843 potentially relevant articles were initially identified. After exclusion of duplicate studies and application of the inclusion criteria, a total of 44 articles were included in the qualitative synthesis (Figure 1). Büning et al. contained three separate case–control studies and Fowler et al. contained two separate case–control studies; therefore, a total of 47 case–control studies involving 18,638 cases and 30,181 controls were included in the final meta-analysis. The main characteristics of these studies are given in Table 1.

Quantitative synthesis
When all the studies were pooled in the meta-analysis, a significant association was seen between \textit{ATG16L1} and Crohn’s disease.

![Flow diagram of the study selection process. CD, Crohn’s disease.](image-url)
| Reference                      | Source of subjects | Genotype and allele distribution (case/control) | HWE                          |
|-------------------------------|--------------------|-----------------------------------------------|------------------------------|
|                               |                    | GG    | GA    | AA    | G     | Conforms | Statistical significance | NOS score |
| Baldassano et al., 200712     | Population-based   | 58/78 | 65/136| 19/67 | 181/292| Yes      | NS                   | 6        |
| Büning et al., 2007:13 study 1| Population-based   | 98/68 | 149/143| 63/74 | 345/279| Yes      | NS                   | 6        |
| Büning et al., 2007:13 study 2| Population-based   | 38/49 | 86/109| 23/49 | 162/207| Yes      | NS                   | 6        |
| Büning et al., 2007:13 study 3| Population-based   | 60/66 | 78/102| 19/47 | 198/234| Yes      | NS                   | 6        |
| Cummings et al., 200714       | Hospital-based     | 209/196| 282/330| 81/157| 700/722| Yes      | NS                   | 6        |
| Prescott et al., 200715       | Population-based   | 435/321| 565/626| 236/288| 1435/1268| Yes     | NS                   | 6        |
| Roberts et al., 200716        | Population-based   | 166/130| 243/285| 87/134| 575/545| Yes      | NS                   | 7        |
| Yamazaki et al., 200717       | Population-based   | 23/32 | 184/167| 274/238| 230/231| Yes      | NS                   | 6        |
| Baptista et al., 200818       | Population-based   | 46/42 | 94/90 | 40/57 | 186/174| Yes      | NS                   | 8        |
| Fowler et al., 2008:19 study 1| Population-based   | 243/339| 315/601| 111/304| 801/1279| Yes     | NS                   | 6        |
| Fowler et al., 2008:19 study 2| Population-based   | 59/110| 73/189| 22/121| 191/409| No       | $P = 0.04$ | 6        |
| Gaj et al., 200820            | Population-based   | 24/32 | 25/70 | 11/37 | 73/134| Yes      | NS                   | 8        |
| Glas et al., 200821           | Population-based   | —     | —     | —     | 906/1673| N/A     | N/A                  | 8        |
| Hancock et al., 200822        | Population-based   | 216/321| 288/569| 82/266| 720/1211| Yes     | NS                   | 7        |
| Lakatos et al., 200823        | Population-based   | 92/33 | 125/83| 49/33 | 309/149| Yes      | NS                   | 7        |
| Lappalainen et al., 200824    | Population-based   | —     | —     | —     | 232/179| N/A     | N/A                  | 6        |
| Latiano et al., 200825        | Population-based   | 227/214| 335/376| 105/159| 789/804| Yes      | NS                   | 7        |
| Okazaki et al., 200826        | Population-based   | 77/88 | 103/150| 28/76 | 257/326| Yes      | NS                   | 8        |
| Perricone et al., 200827      | Population-based   | 33/30 | 73/76 | 57/54 | 139/136| Yes      | NS                   | 7        |
| Peterson et al., 200828       | Population-based   | —     | —     | —     | 655/505| N/A     | N/A                  | 6        |
| Van Limbergen et al., 200829  | Population-based   | 217/98| 294/176| 118/71| 728/372| Yes      | NS                   | 6        |
| Weersma et al., 200830        | Population-based   | 121/280| 125/428| 40/163| 367/988| Yes      | NS                   | 7        |
| Amre et al., 200931           | Population-based   | 102/64| 137/135| 47/91 | 341/263| Yes      | NS                   | 8        |
| Dema et al., 200932           | Population-based   | 178/246| 314/407| 115/206| 670/899| Yes      | NS                   | 7        |
| Dusatkova et al., 200933      | Population-based   | 107/132| 158/239| 68/128| 372/503| Yes      | NS                   | 7        |

(continued)
| Reference                     | Source of subjects | Genotype and allele distribution (case/control) | HWE | Conforms | Statistical significance | NOS score |
|------------------------------|--------------------|-----------------------------------------------|-----|----------|--------------------------|-----------|
| Lacher et al., 2009<sup>34</sup> | Population-based   | GG 60/56 GA 73/128 AA 19/69 G 193/240         | Yes | NS       |                           | 7         |
| Márquez et al., 2009<sup>35</sup> | Population-based   | 125/221 GA 156/347 AA 63/177 G 406/789         | Yes | NS       |                           | 7         |
| Newman et al., 2009<sup>36</sup> | Population-based   | 159/253 GA 204/415 AA 72/227 G 522/921          | No  | P = 0.03 |                           | 9         |
| Palomino-Morales et al., 2009<sup>37</sup> | Hospital-based     | 216/183 GA 253/316 AA 75/167 G 685/682          | Yes | NS       |                           | 7         |
| Cotterill et al., 2010<sup>38</sup> | Population-based   | ——                                         |     |          |                           |           |
| Csöngei et al., 2010<sup>39</sup> | Population-based   | 108/79 GA 151/163 AA 56/72 G 367/321           | Yes | NS       |                           | 7         |
| Gazouli et al., 2010<sup>40</sup>  | Population-based   | 189/161 GA 222/274 AA 63/104 G 600/596         | Yes | NS       |                           | 6         |
| Sventoraiyte et al., 2010<sup>41</sup> | Population-based   | 16/44 GA 28/89 AA 11/53 G 60/177              | Yes | NS       |                           | 8         |
| Fabio et al., 2011<sup>42</sup>  | Population-based   | 94/50 GA 134/97 AA 51/43 G 322/197            | Yes | NS       |                           | 6         |
| Frank et al., 2011<sup>43</sup>  | Hospital-based     | 25/17 GA 22/19 AA 14/23 G 72/53               | No  | P = 0.007 |                         | 5         |
| Lauriola et al., 2011<sup>44</sup> | Population-based   | 6/6 GA 9/11 AA 3/3 G 638/864                 | Yes | NS       |                           | 6         |
| Jung et al., 2012<sup>45</sup>   | Population-based   | ——                                         |     |          |                           |           |
| Wang et al., 2012<sup>46</sup>   | Population-based   | 44/33 GA 164/140 AA 141/179 G 252/206         | Yes | NS       |                           | 6         |
| Hirano et al., 2013<sup>47</sup>  | Population-based   | ——                                         |     |          |                           |           |
| Dalton et al., 2014<sup>48</sup> | Population-based   | 22/8 GA 49/33 AA 12/14 G 93/49                | Yes | NS       |                           | 6         |
| Jakobsen et al., 2014<sup>49</sup> | Population-based   | ——                                         |     |          |                           |           |
| Scolaro et al., 2014<sup>50</sup> | Population-based   | 25/48 GA 53/106 AA 28/84 G 103/202             | Yes | NS       |                           | 8         |
| Serbati et al., 2014<sup>51</sup> | Population-based   | 10/9 GA 43/76 AA 16/30 G 63/94                | No  | P < 0.001 |                         | 6         |
| Zhang et al., 2014<sup>52</sup>  | Population-based   | 77/62 GA 134/166 AA 209/272 G 288/290         | No  | P < 0.001 |                         | 7         |
| Na et al., 2015<sup>53</sup>     | Population-based   | ——                                         |     |          |                           |           |
| Salem et al., 2015<sup>54</sup>  | Hospital-based     | 108/29 GA 78/13 AA 50/15 G 294/71             | No  | P < 0.001 |                         | 6         |
| Yang et al., 2015<sup>55</sup>   | Population-based   | 226/211 GA 838/1033 AA 745/1192 G 1290/1455   | Yes | NS       |                           | 7         |

HWE, Hardy–Weinberg equilibrium; N/A, not available; NOS, Newcastle–Ottawa scale.
NS, not statistically significant (P ≥ 0.05).
in all four genetic models (allelic model: OR = 1.29, 95% CI = 1.22, 1.37, Figure 2; additive model: OR = 1.80, 95% CI = 1.68, 1.92, Figure 3; dominant model: OR = 1.47, 95% CI = 1.39, 1.55, Figure 4; recessive model: OR = 1.46, 95% CI = 1.39, 1.54, Figure 5). When stratified by study design (population- or hospital-based), a significant association between ATG16L1 and Crohn’s disease was still seen in all four genetic models (Table 2).

Sensitivity analyses

Sensitivity analyses were conducted to determine whether modification of the inclusion
criteria of the meta-analysis affected the final results. When the included studies were limited to those conforming to the Hardy–Weinberg equilibrium (P ≥ 0.05), the pooled ORs of these 33 studies were not materially different from those of the full meta-analysis (Table 2). Likewise, when the included studies were limited to those with a high NOS score (≥7), the pooled ORs of these 22 studies were not materially different from those of the full meta-analysis (Table 2).

**Analysis of heterogeneity**

Significant heterogeneity existed in the allelic model (I² = 75.4%). A Galbraith plot was created to graphically assess the source of heterogeneity (Figure 6). The studies by
Yamazaki et al., 17 Fowler et al., 19 (study 1), Latiano et al., 25 Amre et al., 31 Lacher et al., 34 Palomino-Morales et al., 37 Jung et al., 45 and Hirano et al. 47 were identified as contributors to the heterogeneity. When these eight studies were excluded, the $I^2$ was 0.0% and the OR (95% CI) was 1.33 (1.28, 1.37).

**Publication bias**

The shapes of the Begg’s funnel plots did not reveal any evidence of obvious asymmetry (Figure 7). No statistical evidence of publication bias was found using Egger’s regression test ($P = 0.09$ for the allelic model; $P = 0.62$ for the additive model; $P = 0.08$).
for the dominant model; and $P = 0.83$ for the recessive model).

**Discussion**

Since Hampe et al.$^5$ reported in 2007 that *ATG16L1* gene polymorphism was associated with Crohn’s disease, many studies have evaluated the relationship between *ATG16L1* and the risk of Crohn’s disease.$^{56}$ However, the results are inconsistent. As the strength of results from a single case–control study is weak due to small sample sizes, the combination of many studies in a meta-analysis has the benefit of overcoming this limitation by increasing the sample size and

![Figure 5. Forest plot of the association between *ATG16L1* and Crohn’s disease using the recessive model (GG versus GA + AA). The pooled odds ratio (OR) and 95% confidence intervals (CI) are indicated by the diamond. Percentage weights were calculated using a fixed effects model.](image-url)
generating more robust results. Meta-analysis has been widely used in genetic association studies. The present meta-analysis was performed to assess whether the combined evidence supports an association between \textit{ATG16L1} and Crohn's disease.

The present meta-analysis examined \textit{ATG16L1} gene polymorphism and its relationship with the risk of Crohn's disease based on data from 47 case–control studies involving 18,638 cases and 30,181 controls. Most of these studies reported that \textit{ATG16L1} was associated with the risk of Crohn's disease. The ATG16L1 gene polymorphism and its relationship with Crohn's disease have been shown in several studies. The present meta-analysis examined the association between \textit{ATG16L1} and Crohn's disease. This significant association remained in all four genetic models when subgroup analyses were performed based on study design (population-based or hospital-based).

When interpreting the results of this meta-analysis, a number of limitations should be acknowledged. First, it is well known that both environmental factors and individual genetic predisposition contribute to the development of Crohn's disease. Due to the lack of original data, however, the OR, odds ratio; CI, confidence intervals; NOS, Newcastle–Ottawa Scale; HWE, Hardy–Weinberg equilibrium.

| Group analysed | Allelic model (G vs A) | Additive model (GG vs AA) | Dominant model (GG + GA vs AA) | Recessive model (GG vs GA + AA) |
|----------------|-----------------------|---------------------------|---------------------------------|---------------------------------|
|                | OR (95% CI) Analysis model | OR (95% CI) Analysis model | OR (95% CI) Analysis model | OR (95% CI) Analysis model |
| All            | 1.29 (1.22, 1.37) Random effects | 1.80 (1.68, 1.92) Random effects | 1.47 (1.39, 1.55) Fixed effects | 1.46 (1.39, 1.54) Fixed effects |
| Population-based | 1.28 (1.20, 1.37) Random effects | 1.76 (1.64, 1.89) Fixed effects | 1.44 (1.36, 1.52) Fixed effects | 1.46 (1.38, 1.54) Fixed effects |
| Hospital-based  | 1.46 (1.31, 1.62) Fixed effects | 2.18 (1.76, 2.70) Fixed effects | 1.86 (1.54, 2.26) Fixed effects | 1.51 (1.29, 1.76) Fixed effects |
| NOS score ≥ 7  | 1.33 (1.24, 1.43) Random effects | 1.83 (1.68, 1.99) Fixed effects | 1.49 (1.39, 1.59) Fixed effects | 1.47 (1.37, 1.57) Fixed effects |
| Conform to HWE | 1.32 (1.24, 1.40) Random effects | 1.79 (1.67, 1.92) Fixed effects | 1.46 (1.38, 1.54) Fixed effects | 1.46 (1.38, 1.54) Fixed effects |
Figure 6. Galbraith plot of the allelic model. The outliers were the studies by Yamazaki et al., Fowler et al. (study 1), Latiano et al., Amre et al., Lacher et al., Palomino-Morales et al., Jung et al. and Hirano et al., effect estimate; se, standard error.

Figure 7. Begg’s funnel plots with pseudo 95% confidence limits of all studies in the meta-analysis using the four model types: (a) allelic model (G allele versus A allele); (b) additive model (GG versus AA); (c) dominant model (GG + GA versus AA); (d) recessive model (GG versus GA + AA). SE, standard error; OR, odds ratio.
potential interactions between these two types of influence has not been evaluated. Secondly, \textit{ATG16L1} seems to exert a close functional correlation with other genes in regulating autophagy. For example, the interaction of \textit{ATG16L1} and \textit{NOD2} has been implicated in the pathogenesis of Crohn’s disease.\textsuperscript{63} Potential gene–gene interactions require further evaluation. Thirdly, the \textit{ATG16L1} genotype has been reported to be associated with disease phenotype,\textsuperscript{65} which has clinical significance. Further combined analyses are needed to clarify the association between the \textit{ATG16L1} genotype and Crohn’s disease phenotype.

In conclusion, the present meta-analysis of robust data and unbiased results demonstrated an association between \textit{ATG16L1} genotype and the development of Crohn’s disease. These findings will be helpful in understanding the aetiology of Crohn’s disease and indicate that the \textit{ATG16L1} gene might have potential as a therapeutic or diagnostic target.

\section*{Declaration of conflicting interest}
The authors declare that there is no conflict of interest.

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