ZNF133 is associated with infliximab responsiveness in patients with IBD using whole-exome sequencing

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Disclosure
No conflict of interest
Background

• Infliximab has been widely prescribed for treating IBD
• Response rate to infliximab differ among patients
  • Primary nonresponse: 10-40% patients
  • Loss of response: 24-46% patients
• Predictors of nonresponse
  • Anti-drug antibody, serum drug level
  • Genetic markers: FCGR3A, TLR2, TLR4, TLR9, TNFRSF1A, IFNG, IL6, and IL1B

• Aim: Identification of genetic and clinical markers that predict infliximab response.

Methods

• 139 Korean IBD patients
  • Whole-exome sequencing data
  • Clinical data
  • Primary nonresponse
    • 14 weeks after induction therapy
  • Loss of response
    • Infliximab use >6 months

• Replication
  • 77 German IBD patients
  • Whole-exome sequencing data

• Primary nonresponse do NOT meet any criteria:
  1) ↓CDAI > 70 from baseline
  2) Improvement in anal fistula
  3) ↓Mayo score >30% and ↓0-1 or in rectal bleeding score >1

• Loss of response
  1) Disease flare up (CDAI ≥220, Mayo ≥6)
  2) Addition of other IBD drugs due to disease aggravation
  3) Increase in the dose or shortening of the interval of IFX
  4) Change of IFX to another biologics
  5) Relapse evidence on endoscopy
Primary nonresponse

• Screening: 5 candidate variants \( (P < 5 \times 10^{-6}) \)

• Validation
  • rs2228273 in ZNF133 was validated (Combined \( P = 6.49 \times 10^{-7} \))
Primary nonresponse

- Multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Primary nonresponse</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2.05 (0.52–8.01)</td>
<td>0.302</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0.99 (0.94–1.05)</td>
<td>0.800</td>
</tr>
<tr>
<td>Concurrent medication use (azathioprine or 6-mercaptopurine)</td>
<td>4.78 (1.16–19.76)</td>
<td>0.031*</td>
</tr>
<tr>
<td>Infliximab indication</td>
<td>1.43 (0.67–3.06)</td>
<td>0.352</td>
</tr>
<tr>
<td>Body weight at 1st infliximab infusion (&lt;50 kg)</td>
<td>5.26 (1.42–19.54)</td>
<td>0.013*</td>
</tr>
<tr>
<td>rs2228273</td>
<td>11.94 (3.81–37.39)</td>
<td>2.10E-05*</td>
</tr>
</tbody>
</table>
## Loss of response

- Multivariate logistic regression in Crohn’s disease patients

<table>
<thead>
<tr>
<th>Loss of response in CD</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.279 (0.411–3.983)</td>
<td>0.671</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0.995 (0.928–1.065)</td>
<td>0.875</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.998 (0.988–1.008)</td>
<td>0.726</td>
</tr>
<tr>
<td>CDAI at 1st infliximab infusion</td>
<td>1.011 (1.002–1.020)</td>
<td>0.017*</td>
</tr>
<tr>
<td>rs9144</td>
<td>3.794 (1.634–8.808)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

CDAI: Crohn’s disease activity index
Conclusions

• We identified clinical and genetic markers associated with infliximab response in patients with IBD

• *ZNF133* could be used as a predictor for treatment response to infliximab in trans-ethnic populations

• Our findings could provide insights to maximize the efficacy of infliximab therapy in IBD
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