Causal relationships between genetically determined metabolites and human intelligence: A Mendelian randomization study

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Abstract

Intelligence predicts important life and health outcomes, but the biological mechanisms underlying differences in intelligence are not yet understood. The use of genetically determined metabotypes (GDMs) to understand the role of genetic and environmental factors, and their interactions, in human complex traits has been recently proposed. However, this strategy has not been applied to human intelligence. Here we implemented a two-sample Mendelian randomization (MR) analysis using GDMs to assess the causal relationships between genetically determined metabolites and human intelligence. The standard inverse-variance weighted (IVW) method was used for the primary MR analysis and three additional MR methods (MR-Egger, weighted median, and MR-PRESSO) were used for sensitivity analyses. Using 25 genetic variants as instrumental variables (IVs), our study found that 5-oxoproline was associated with better performance in human intelligence tests (P {IVW} = 9.25 × 10^{-5}). The causal relationship was robust when sensitivity analyses were applied (P MR-Egger = 0.0001, P Weighted median = 6.29 × 10^{-6}, P MR-PRESSO = 0.0007), and no evidence of horizontal pleiotropy was observed. Similarly, also dihomo-linoleate (20:2n6) and p-acetamidophenylglucuronide showed robust association with intelligence. Our study provides novel insight by integrating genomics and metabolomics to estimate causal effects of genetically determined metabolites on human intelligence, which help to understanding of the biological mechanisms related to human intelligence.

Introduction

Intelligence affects all aspects of human life [1]. During the school years, some individuals show higher intelligence, attain better marks in exams, and have better prospects for further education [2,3]. In the workplace, intelligence influences performance, efficiency, the ability to cope with difficulties, and career achievements [4]. Intelligence is also a predictor of higher quality of life and better health outcomes [5,6]. Revealing the biological bases of individual differences in human intelligence has become a central and enduring aim of psychological and brain sciences. During the past decade, advances in genetic research have greatly promoted our understanding of intelligence [7-10]. However, further insight on its biological basis is needed.

Understanding the role of genetic characteristics and their interaction with environmental factors is the key to reveal the biological mechanisms underlying differences in human intelligence [11]. Currently, omics technologies (such as genomics, metabolomics, etc.) are widely used to provide a comprehensive characterization at the molecular level of the human body as a biological system. These approaches have successfully identified a number of informative biomarkers and greatly advanced our knowledge of the molecular mechanisms responsible for many traits. However, most omics studies focus only on a single layer, and therefore fail to capture information across multiple omics assays [12]. Recently, researchers have linked metabolomics traits to genomic information through genome-wide association studies (GWAS) on non-targeted metabolic profiling [13-15]. A large database of genetically determined metabolotypes (GDMs) has been thus established to provide comprehensive insights of how genetic variation influences metabolism [16]. The established GDMs provide important intermediates to reveal the role of the interactions between genetics and metabolic traits in determining differences in human intelligence.

Mendelian randomization (MR) is a novel genetic epidemiology study design using genetic variants associated with a modifiable exposure or biological intermediate as instrumental variables (IVs) to estimate the causality of an agent on clinical outcomes of interest [17]. By making use of inherent genetic variants as proxies, the MR design can avoid the potential confounding factors that are common in conventional observational studies [18]. In recent years, the explosion in the number of published GWAS summary data has increased the popularity of MR approaches (and in particular of two-sample MR analysis) as tools to infer the causality of risk factors on complex health outcomes [19-21]. In this study, using GDMs and the results of GWAS on intelligence, we implement two-sample MR analysis to: (1) assess the causal effects of genetically determined metabolites on human intelligence; (2) investigate the genetic basis that may play a central role in determining the variation of the related metabolites and the differences in human intelligence; (3) identify potential metabolic pathways involved in the biological processes related to intelligence.

Methods

GWAS scans with metabolomics traits

Shin et al. reported the most comprehensive exploration of genetic influences on human metabolism so far, by performing a GWAS of non-targeted metabolomics on 7824 healthy adults [16]. Metabolic profiling was carried out on fasting serum using high-performance liquid chromatography and gas chromatography separation coupled with tandem mass spectrometry. After quality control, 486 metabolites were retained for genetic analysis, among which 309 were chemically identified and could be further assigned to 8 metabolic groups (amino acids, carbohydrates, cofactors and vitamins, energy, lipids, nucleotides, peptides, and xenobiotics), while the other 177 were classified as ‘unknown’. The final genome-wide association analyses were carried out on approximately 2.1 million single nucleotide polymorphisms (SNPs). Full summary statistics for the 486 metabolites can be found at the Metabolomics GWAS Server (http://metabolomics.helmholtz-muenchen.de/gwas/).

IVs for the 486 metabolites

The foundational principle of MR relies on the existence of valid IVs. A genetic variant is a valid IV if it is (i) significantly associated with the exposure, (ii) independent of confounders, and (iii) associated with the outcome only through the exposure [22]. To identify valid IVs, we first selected the SNPs with significance P < 1 × 10^{-5}, so as to account for a proportion as large as possible of the variance explained for the corresponding metabolite. We next performed a clumping procedure (linkage disequilibrium threshold of r^2 < 0.1 within a 500-kb window) to select the independent SNPs using the PLINK software (v1.9). To avoid the negative impact of weak IVs, we further used the proportion of variation explained by each IV (R^2) and the F statistics to select SNPs strong enough to be valid IVs. Typically, an F statistic >10 is considered sufficient for MR analysis [23].

GWAS summary data on intelligence
GWAS summary statistics for intelligence were obtained from the study by Savage et al. [10]. Briefly, these authors performed a large GWAS meta-analysis of 269,867 individuals from 14 cohorts of European ancestry. Intelligence was assessed using different neurocognitive tests and the general factor of intelligence (Spearman’s $r$). Although differences in assessment methods might reduce the power to detect associations in meta-analyses, this approach can at the same time reduce type I errors by removing measurement errors, and therefore identify SNPs with robust associations to the common latent factor underlying intelligence across different methods. Stringent quality control procedures were applied to the summary statistics for each cohort. Association analysis was conducted controlling for covariates of age, sex, genotyping array, socioeconomic status for specific cohort, and twenty European-based ancestry principal components. Finally, a total of 9,295,118 SNPs were included in the meta-analysis. Notably, the Davies et al. reported another GWAS for intelligence with a larger sample size, but the summary data for the full dataset is not available due to data permissions.

Statistical analysis

Primary two-sample MR analyses were performed using the standard inverse-variance weighted (IVW) method. The IVW method provides a consistent estimate of causal effects by combining the ratio estimates of each variant in a fixed-effect meta-analysis model [23]. The P-value was calculated with a standard normal cumulative distribution function on the ratio of the combined causal effect and its standard error. The significance threshold to declare a causal relationship for the IVW-based MR estimate was set, using Bonferroni correction, at $P < 1.03 \times 10^{-4} (= 0.05/486)$. Associations with $P < 0.05$, but not reaching the Bonferroni-corrected threshold, were reported as suggestive of association.

The IVW method provides an unbiased estimate under the assumption that all genetic variants are valid IVs. However, this assumption is easily violated, leading to inaccurate estimates, when horizontal pleiotropy occurs (some variants act on the outcome via a different intermediary) [24]. To avoid the effects of widespread horizontal pleiotropy in MR, we further performed sensitivity analyses using three additional MR methods: the MR-Egger method, which provides a consistent causal effect estimate, even when all genetic variants violate the assumptions defining valid IVs, under a weaker assumption (known as the InSIDE [instrument strength independent of direct effect] assumption) [24]; the weighted median method, which introduces a weighted median estimator and provides a more precise estimate than MR-Egger regression without the InSIDE assumption [25], and the MR-PRESSO method, a newly developed approach which can identify and correct for horizontal pleiotropic outliers in MR [26]. We further used the MR-PRESSO global test as well as the intercept of the MR-Egger regression to test for pleiotropy, and we also evaluated heterogeneity with the $I^2$ and the Cochran Q test. Typically, $I^2 > 25\%$ or Cochran Q-derived $P < 0.05$ were used as indicators of possible horizontal pleiotropy. Analyses were carried out using the packages MendelianRandomization and MR-PRESSO in R (version 3.6.1).

Metabolic pathway analysis

Metabolic pathway analysis was carried out using the web-based tool suite MetaboAnalyst 4.0 (http://www.metaboanalyst.ca/) [27]. For this analysis, we extracted all metabolites showing suggestive associations in the IVW estimates ($P_{IVW} < 0.05$). Two libraries of metabolic pathways or metabolite sets were selected for enrichment analysis, namely the Small Molecule Pathway Database (SMPDB, http://www.smpdb.ca) [28] and the Kyoto Encyclopedia of Genes and Genomes (KEGG, https://www.kegg.jp/) database [29]. P-values < 0.05 were considered statistically significant.

Results

Causal effects of the metabolites on intelligence

We selected 3–675 independent genetic variants as IVs for each of the 486 metabolites (Supplementary Table 1). On average, the IVs explained 4.7% (range 0.8–83.5%) of the variance of their respective metabolic traits. The minimum F statistic used to evaluate the strength of these IVs was 20.33. Using these IVs, we selected for enrichment analysis, namely the Small Molecule Pathway Database (SMPDB, http://www.smpdb.ca) [28] and the Kyoto Encyclopedia of Genes and Genomes (KEGG, https://www.kegg.jp/) database [29]. P-values < 0.05 were considered statistically significant.

Sensitivity analysis

Table 1 shows the results of the sensitivity analysis for the 16 IVW-identified known metabolites. The causal relationship between 5-oxoproline and intelligence was robust when additional MR methods were applied ($P_{MR-Egger} = 0.0001$, $P_{Weighted\, median} = 6.29 \times 10^{-5}$, $P_{MR-PRESSO} = 0.0007$), and no horizontal pleiotropy was observed ($P_{intercept} = 0.09$, $P_{Global\, test} = 0.06$, $I^2 = 25\%$, $P_{Heterogeneity} = 0.13$). Two other metabolites also showed robust associations with intelligence, namely dihomo-linoleate (20:2n6) ($P_{MR-Egger} = 0.0494$, $P_{Weighted\, median} = 0.0236$, $P_{MR-PRESSO} = 0.0293$, $P_{Global\, test} = 0.16$) and p-acetamidophenylglucuronide ($P_{MR-Egger} = 0.0075$, $P_{Weighted\, median} = 0.0060$, $P_{MR-PRESSO} = 0.0454$, $P_{Global\, test} = 0.0611$), and there were no evidence of horizontal pleiotropy ($P_{intercept} = 0.24$, $P_{Global\, test} = 0.17$, $I^2 = 0\%$, $P_{Heterogeneity} = 0.96$ for dihomo-linoleate (20:2n6) and $P_{intercept} = 0.06$, $P_{Global\, test} = 0.06$, $I^2 = 17\%$, $P_{Heterogeneity} = 0.13$ for p-acetamidophenylglucuronide; Table 1). Funnel plots appeared generally symmetrical for all the three metabolites, also suggesting no evidence for horizontal pleiotropy (Supplementary Figure 1). Dihomo-linoleate (20:2n6) showed a negative association with intelligence ($b_{IVW} = -0.14$; 95% CI: -0.25 to -0.04), while the association between p-acetamidophenylglucuronide and intelligence was positive ($b_{IVW} = 0.01$; 95% CI: 0.00 to 0.01). The causal association between 5-oxoproline and human intelligence is shown on Figure 2, while the associations for dihomo-linoleate (20:2n6) and p-acetamidophenylglucuronide with intelligence are represented on Figure 3. Notably, the very small effect size for p-acetamidophenylglucuronide on intelligence might limit its potential utility as a biomarker.
Genetic basis for the causal associations

We further investigated the genetic variants that affected both metabolite levels and intelligence. Table 2 shows the 25 SNPs used as IV of 5-oxoproline. Among them, rs11986602 showed the most significant association with 5-oxoproline ($\beta = 0.0620; \ SE = 0.0029, P = 6.29 \times 10^{-104}$). Notably, it also showed a strong association signal with intelligence ($\beta = -0.0196; SE = 0.0044, P = 9.53 \times 10^{-6}$). Moreover, this SNP had the largest effect sizes on both 5-oxoproline and intelligence, suggesting that the related genetic locus might provide valuable information on the biological mechanisms of intelligence, and that 5-oxoproline might be an important functional intermediate to understand the biological process through which genetics affects intelligence. The IVs for dihomo-linoleate (20:2n6) and p-acetamidophenylglucuronide are shown in Supplementary Table 3 and Supplementary Table 4.

Metabolic pathway analysis

Table 3 shows the results of the metabolic pathway analysis. Based on the 16 known metabolites identified by the IVW method, we detected only one significant metabolic pathway associated with intelligence, namely Alpha linolenic acid and linoleic acid metabolism ($P = 0.0062$). Two metabolites identified by IVW, docosapentaenoate (n3 DPA; 22:5n3) and linolenate (18:3n3 or 6), are involved in Alpha linolenic acid and linoleic acid metabolism according to the SMPDB database. Importantly, many of the metabolites found by our analysis have not been assigned to any metabolic pathway currently recorded in the SMPDB or KEGG databases. Extensive further research will be needed to explore whether these metabolites are involved in biological processes relevant to differences in human intelligence.

Discussion

We implemented a two-sample MR analysis to assess the causal relationships between genetically determined metabolites and human intelligence. Using genetic variants as IVs, we found that the genetically determined levels of 5-oxoproline were associated with better performance in human intelligence tests. This causal relationship was confirmed by sensitivity analyses. Our study also identified other metabolites and metabolic pathways involved in biological processes related to human intelligence, such as dihomo-linoleate (20:2n6) and p-acetamidophenylglucuronide. To the best of our knowledge, this is the first study combining information from genomics and metabolomics to assess the causal effects of metabolome traits on human intelligence.

5-oxoproline, also known as pyroglutamic acid, is a cyclized derivative of L-glutamic acid that participates substantially in the glutamate and glutathione metabolism [30]. Disturbances in glutamate and glutathione metabolism can lead to a series of neurologic phenotypes, including developmental delay, ataxia, seizures, and intellectual disability [31]. Moreover, 5-oxoproline was also developed and sold as an over-the-counter “smart drug” for cognitive and memory improvement [32,33]. However, it was also demonstrated that metabolic acidosis could be caused by excessive 5-oxoproline generation, with multiple adverse effects on many organ systems [34]. Our study found that elevated levels of 5-oxoproline were associated with a higher score in intelligence tests, supporting the potential usefulness of 5-oxoproline in improving intelligence-related performance. However, more work aimed at understanding the molecular mechanisms involved is needed to further clarify the role of this compound in human intelligence.

Genetic factors played a central role in our study of the causal relationship between metabolic traits and intelligence. The SNP rs11986602 (corresponding to the EXOSC4 gene) was the most significantly associated to both 5-oxoproline levels and human intelligence. Although rarely discussed in the past literature, EXOSC4 is known to be related to the protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK, encoded by the EIF2AK3 gene), which regulates gene expression [35]. A recent study reported that locally reduced PERK expression or activity could enhance neuronal excitability and improve memory and cognitive function in young mice [36]. Another study provided evidence that PERK is a key regulator of memory impairments and neurodegeneration in Alzheimer's disease [37]. Thus, EXOSC4 might be a causal risk gene participating in physiological processes important for human intelligence.

We further focused on the metabolic pathways that might be involved in the biological processes associated to human intelligence. The only identified metabolic pathway in our study was Alpha linolenic acid and linoleic acid metabolism. Alpha linolenic acid and linoleic acid are long-chain polyunsaturated fatty acids, which are essential nutrients in the development and functioning of the brain [38]. Many related compounds, such as alpha linolenic acid and docosahexaenoic acid, are involved in the rapid growth and development of the infant brain [39,40]. Our study thus reinforced the importance of alpha linolenic acid and linoleic acid metabolism for human intelligence, providing valuable information for understanding the biological mechanisms related to human intelligence.

The current study has several strengths. First, we implemented a novel MR study design to assess the causal relationships between genetically determined metabolites and human intelligence. By using genetic variants as IVs, the MR approach prevents confounding, reverse causation, and various biases common in observational epidemiological studies. Second, our study provides, indirectly, a comprehensive assessment of the causal effects of metabolites assessed in observational epidemiological studies. Second, our study could not avoid the bias of dynastic effect, which almost certainly violated the independence assumption of MR, as they induced a correlation between the environment a child is raised in and their genetic inheritance [44,45]. This is a challenge in MR studies and we have tried our best to provided informative evidence using various MR methods. Furthermore, we will implement experimental studies to verify the findings of the present MR estimates in our future analysis. Third, the MR estimates from non-experimental date could not provide information towards molecular mechanism, further work should be done to determine the roles of metabolites or genetic variants in development of intelligence.
In summary, our study identified multiple metabolites that might have causal effects on human intelligence, among which 5-oxoproline presented significant association signals after Bonferroni correction. The association was shown to be robust by sensitivity analyses. Our study also highlighted that genetic factors (e.g. the EXOSC4 gene) contributed substantially to the variation of metabolite levels and differences in human intelligence. Moreover, our findings suggest that alpha linolenic acid and linoleic acid metabolism might be involved in the biological processes underlying intelligence. Though further evidence from experimental data is needed, our study provides novel clues that could improve our understanding of the biological mechanisms related to human intelligence.

**Abbreviations**

GDM: genetically determined metabotype; MR: Mendelian randomization; IVW: inverse-variance weighted; IV: instrumental variable; GWAS: genome-wide association study; SNP: single nucleotide polymorphism; InSIDE: instrument strength independent of direct effect; SMPDB: Small Molecule Pathway Database; KEGG: Kyoto Encyclopedia of Genes and Genomes

**Declarations**

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**Availability of data and materials**

Full summary statistics for the 486 metabolites are publicly available at the Metabolomics GWAS Server (http://metabolomics.helmholtz-muenchen.de/gwas/). GWAS summary statistics for intelligence are download from http://ctg.cnrc.nl/software/summary_statistics.

**Authors’ contributions**

XM and JY were responsible for the study conception and study design. BZ, LQ, FG and YF performed the data collation and statistical analysis. JY and BZ drafted the manuscript. QM and LY were involved in the technical supports. BY and WW contributed to interpretation and editing of the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

All authors read and approved the final manuscript.

**Competing interests**

The authors have no conflict of interest.

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### Tables

**Table 1** Sensitivity analysis of causal associations between metabolites and intelligence

| Metabolites                  | MR-Egger β (95% CI) | P-value | Weighted median β (95% CI) | P-value | MR-PRESSO β (95% CI) | P-value | Pleiotropy test | F |
|------------------------------|---------------------|---------|----------------------------|---------|----------------------|---------|-----------------|---|
| **Amino acid**               |                     |         |                            |         |                      |         |                 |   |
| 5-oxoproline                 | 0.36(0.18,0.55)     | 0.0001  | 0.31(0.18,0.45)            | 6.29E-06| 0.24(0.12,0.35)      | 0.0007  | 0.09            | 0.06| 2   |
| indolelactate                | -0.11(-0.27,0.06)   | 0.2135  | -0.11(-0.23,0.02)          | 0.0872  | -0.09(-0.17,-0.02)   | 0.0244  | 0.85            | 0.76| (  |
| **Carbohydrate**             |                     |         |                            |         |                      |         |                 |   |
| mannitol                     | -0.01(-0.07,0.06)   | 0.9040  | -0.02(-0.06,0.02)          | 0.2799  | -0.03(-0.06,-0.01)   | 0.0138  | 0.34            | 0.84| (  |
| **Lipid**                    |                     |         |                            |         |                      |         |                 |   |
| 2-oleoylglycerophosphocholine| -0.37(-0.82,0.08)   | 0.1067  | 0.21(0.05,0.37)            | 0.0117  | 0.18(0.05,0.30)      | 0.0141  | 0.26            | 0.01| 1   |
| palmitoylglycerophosphocholine| 0.06(-0.11,0.24)  | 0.4860  | 0.11(-0.01,0.23)           | 0.0682  | 0.14(0.04,0.25)      | 0.0117  | 0.26            | <0.01| 4 |   |
| 2-stearoylglycerophosphocholine| -0.01(-0.39,0.38) | 0.9734  | 0.11(-0.01,0.22)           | 0.0554  | 0.11(0.03,0.20)      | 0.0265  | 0.54            | 0.43|   |
| dhomo-linoleate (20:2n6)     | -0.33(-0.66,-0.01)   | 0.0494  | 0.17(-0.32,-0.02)          | 0.0236  | -0.14(-0.25,-0.04)   | 0.0293  | 0.24            | 0.17| (  |
| docosapentaenoate (22:5n3)   | 0.16(+0.03,0.40)    | 0.0993  | 0.16(-0.28,-0.03)          | 0.0117  | -0.16(-0.29,-0.03)   | 0.0414  | <0.01           | <0.01| 7 |   |
| linolenate (18:3n3 or 6)     | -0.37(-0.73,-0.01)   | 0.0414  | -0.19(-0.38,-0.01)         | 0.0497  | -0.20(-0.38,-0.03)   | 0.0814  | 0.30            | 0.08| '  |
| acetylcarnitine              | -0.17(-0.54,0.20)   | 0.3618  | -0.23(-0.39,-0.07)         | 0.0053  | -0.25(-0.40,-0.10)   | 0.0044  | 0.66            | 0.01| 5   |
| **Peptide**                  |                     |         |                            |         |                      |         |                 |   |
| cyclo(leu-pro)               | -0.09(-0.19,0.02)   | 0.1018  | -0.03(-0.10,0.04)          | 0.4332  | -0.06(-0.12,-0.01)   | 0.0438  | 0.60            | 0.03| 3   |
| **Xenobiotics**              |                     |         |                            |         |                      |         |                 |   |
| stachydrine                  | 0.10(+0.05,0.25)    | 0.2068  | 0.04(-0.02,0.10)           | 0.1482  | 0.06(0.02,0.11)      | 0.0308  | 0.65            | 0.41| 1   |
| p-acetamidophenylglucuronide | 0.01(0.00,0.01)     | 0.0075  | 0.01(0.00,0.01)            | 0.0060  | 0.01(0.00,0.01)      | 0.0454  | 0.06            | 0.06| 1   |
| salicylicuric glucuronide    | 1.00(0.98,1.02)     | 0.7825  | 0.99(0.97,1.01)            | 0.1379  | 0.99(0.98,0.99)      | 0.0373  | 0.05            | 0.48| (  |
| hydroquinone sulfate         | 0.97(0.94,1.01)     | 0.204   | 0.97(0.94,1.01)            | 0.0865  | 0.98(0.96,0.99)      | 0.0211  | 0.96            | 0.69| (  |
| SNP         | Gene     | CHRA1A25-oxoproline | Intelligence |
|------------|----------|---------------------|--------------|
|            | Beta     | SE                  | P-value      | Beta     | SE          | P-value     |
| rs11986602EXOSC4 | A        | T                   | -0.062000.00291.07E-104 | 0.019600.00449.53E-06 |            |            |            |
| rs9987070  | C        | G                   | -0.028000.00592.43E-06 | -0.008300.00710.2381 |            |            |            |
| rs10890517 | T        | C                   | -0.019700.00433.45E-06 | -0.013900.00690.0427 |            |            |            |
| rs5764925  | A        | G                   | -0.016000.00311.91E-07 | -0.002100.00500.6782 |            |            |            |
| rs13159409 | P        | A                   | 0.014000.00291.07E-06 | 0.001900.00410.6478 |            |            |            |
| rs12294182MICAL2 | C    | T                   | -0.014800.00322.74E-06 | -0.007500.00530.1535 |            |            |            |
| rs2068157  | G        | C                   | 0.013700.00318.99E-06 | -0.003700.00480.4362 |            |            |            |
| rs9964014  | A        | C                   | -0.013200.00251.80E-07 | -0.006000.00780.4388 |            |            |            |
| rs11605366 | C        | T                   | -0.012200.00277.55E-06 | -0.011100.00430.0094 |            |            |            |
| rs12143589 | A        | G                   | 0.011800.00233.38E-07 | -0.002400.00360.5034 |            |            |            |
| rs13013224LOC1053691652 | C | G                   | 0.011300.00237.04E-07 | -0.003100.00350.3781 |            |            |            |
| rs306676   | A        | G                   | 0.011200.00242.48E-06 | -0.002700.00410.5047 |            |            |            |
| rs9650466  | M        | R                   | 0.011000.00203.80E-08 | 0.004600.00280.0938 |            |            |            |
| rs1001210  | T        | C                   | -0.016000.00233.80E-06 | -0.005100.00370.1678 |            |            |            |
| rs17017431TRAF5 | A  | T                   | 0.010500.00233.80E-06 | 0.002200.00380.5628 |            |            |            |
| rs10853533SLC14A2 | A | C                   | 0.010300.00236.09E-06 | -0.006800.00430.1133 |            |            |            |
| rs2115151  | S        | P                   | 0.010300.00223.75E-06 | 0.002400.00410.5561 |            |            |            |
| rs7015048  | T        | C                   | 0.010000.00153.16E-11 | -0.001500.00280.5864 |            |            |            |
| rs9460424  | G        | T                   | -0.009700.00229.16E-06 | -0.005300.00350.1328 |            |            |            |
| rs4646693  | L        | R                   | -0.009000.00206.80E-06 | -0.000100.00540.9909 |            |            |            |
| rs8092658  | S        | L                   | -0.009000.00206.80E-06 | 0.000100.00280.9828 |            |            |            |
| rs1578743  | A        | C                   | 0.007500.00161.70E-06 | 0.002600.00290.3664 |            |            |            |
| rs7973508  | A        | G                   | -0.007300.00165.40E-06 | 0.000700.00300.8245 |            |            |            |
| rs12464424 | C        | T                   | -0.007100.00167.47E-06 | 0.005500.00300.0651 |            |            |            |
| rs12611788GALNT14 | T | C                   | -0.007000.00155.51E-06 | -0.006200.00290.0301 |            |            |            |
Table 3
Results of metabolic pathway analysis

| Metabolic Pathway                                      | Involved Metabolites                        | P value | Database |
|--------------------------------------------------------|---------------------------------------------|---------|----------|
| Alpha linolenic acid and linoleic acid metabolism       | Docosapentaenoate (n3 DPA; 22:5n3); 0.0062   | 0.0062  | SMPDB    |
|                                                         | Linolenate (18:3n3 or 6)                    |         |          |
| Alpha-linolenic acid metabolism                        | Linolenate (18:3n3 or 6)                    | 0.0702  | KEGG     |
| Glutathione metabolism                                 | Linolenate (18:3n3 or 6)                    | 0.0912  | KEGG     |
| Beta oxidation of very long chain fatty acids           | Acetylcarnitine                             | 0.0989  | SMPDB    |
| Fructose and mannose metabolism                        | Mannitol                                    | 0.1140  | KEGG     |
| Oxidation of branched chain fatty acids                 | Acetylcarnitine                             | 0.1622  | SMPDB    |
| Tryptophan metabolism                                  | Indolelactate                               | 0.1816  | KEGG     |

Figures

**Metabolites** | **SNPs** | **β (95% CI)** | **Lower Risk** | **Higher Risk** | **P Value** |
---|---|---|---|---|---|
**Amino acid** | | | | | |
5-oxoproline | 25 | 0.24(0.12 to 0.35) | | | 9.25E-05 |
Indolelactate | 17 | -0.09(-0.18 to -0.01) | | | 0.0313 |
**Carbohydrate** | | | | | |
mannitol | 13 | -0.03(-0.06 to -0.01) | | | 0.0223 |
**Lipid** | | | | | |
2-oleoylglycerophosphocholine | 16 | 0.18(0.05 to 0.30) | | | 0.0055 |
2-palmitoylglycerophosphocholine | 24 | 0.14(0.04 to 0.25) | | | 0.0062 |
2-stearoylglycerophosphocholine | 13 | 0.11(0.03 to 0.20) | | | 0.0114 |
1-oleoylglycerol (1-monolein) | 16 | 0.09(0.01 to 0.17) | | | 0.0359 |
dihomo-linoleate (20:2n6) | 9 | -0.14(-0.25 to -0.04) | | | 0.0081 |
docosapentaenoate (n3 DPA; 22:5n3) | 11 | -0.16(-0.29 to -0.03) | | | 0.0194 |
linolenate (18:3n3 or 6) | 5 | -0.20(-0.38 to -0.03) | | | 0.0205 |
acetylcarnitine | 19 | -0.25(-0.40 to -0.10) | | | 0.0011 |
**Peptide** | | | | | |
cyclo(leu-pro) | 15 | -0.06(-0.12 to -0.01) | | | 0.0267 |
**Xenobiotics** | | | | | |
stachydrine | 7 | 0.06(0.02 to 0.11) | | | 0.0050 |
p-acetamidophenylglucuronide | 63 | 0.01(0.00 to 0.01) | | | 0.0411 |
salicylic glucuronide | 13 | -0.01(-0.02 to -0.01) | | | 0.0192 |
hydroquinone sulfate | 17 | 0.98(0.95,0.99) | | | 0.0208 |

Figure 1
Mendelian randomization associations of genetically determined metabolites on intelligence.
Figure 2

Genetic associations between 5-oxoproline and intelligence.

Figure 3

Genetic associations of two suggestive metabolites with intelligence. a. dihomo-linoleate (20:2n6); b. p-acetamidophenylglucuronide.

Supplementary Files

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- SupplementaryTables.xlsx
- SupplementaryTables.xlsx
- SupplementaryFigure1.pdf
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