Cell Genomics

CellPress
OPEN ACCESS

Preview

Expanding the genetic landscape of obesity

Jian Yang[1,2,*]
[1]School of Life Sciences, Westlake University, Hangzhou, Zhejiang 310030, China
[2]Westlake Laboratory of Life Sciences and Biomedicine, Hangzhou, Zhejiang 310024, China
*Correspondence: jian.yang@westlake.edu.cn
https://doi.org/10.1016/j.xgen.2023.100400

In a recent *Cell Genomics* article, Kaisinger, Kentistou, Stankovic, et al.[1] use a large-scale exome sequencing study in the UK Biobank to identify rare gene variants associated with sex-specific and life-course effects on obesity. Jian Yang discusses the authors' findings and wider context in obesity research in this preview.

Obesity, characterized by an excess of body mass index (BMI), is a global health concern that is closely linked to leading causes of mortality, such as cardiovascular diseases, diabetes, and certain cancers.[2] Unraveling the genes responsible for variability in BMI holds great promise in gaining new insights into the biological processes underlying obesity, thereby facilitating the development of targeted interventions and therapies for obesity. Genome-wide association studies (GWASs) have identified hundreds of loci harboring common genetic variants associated with BMI,[3,4] and as the sample sizes of GWASs continue to grow, it is expected that more loci will be discovered. However, the lead variant at a GWAS locus is often not causal (Figure 1), primarily due to the complex linkage disequilibrium (LD) structure of common variants and the uncertainties in test statistics arising from sampling, genotyping errors, and imputation inaccuracies.[5,6] Moreover, the GWAS signals are often located in non-coding regions of the genome, posing challenges in determining the causal genes responsible for the observed genetic associations.[7] These obstacles have impeded the translation of genetic associations discovered in GWASs into biological mechanisms and medicine.

Conventional GWASs have focused on common variants due to the underrepresentation of rare variants on SNP arrays. The application of whole-exome or whole-genome sequencing at the cohort level has opened new opportunities for studying associations of rare variants with complex traits, including diseases. Using whole-exome sequencing data for rare variant association analysis offers two significant advantages. Firstly, unlike common variants, rare variants often do not have strong LD with other variants; therefore, the top associated rare variants are likely to be causal[5] (Figure 1). Secondly, the trait-associated rare variants often exhibit larger effect sizes and are more likely to reside in coding regions of the genome compared to common variants. These characteristics facilitate the identification of causal genes, streamlining the process of uncovering the underlying molecular mechanisms driving the genetic associations.

One aspect often overlooked in genetic association studies is the dependency of genetic effects on factors such as age, sex, or environmental conditions. Failing to account for these factors can lead to a decrease in power to detect the context-dependent genetic effects. To address this, Kaisinger et al.[1] conducted sex- and age-stratified exome-wide association studies (ExWASs) in up to 419,692 individuals from the UK Biobank. The authors focused only on variants with a minor allele frequency <0.1% in two overlapping functional categories: (1) protein truncating variants (PTVs) and (2) damaging variants (DMGs), including missense variants with a CADD score $\geq$ 25 and PTVs. The analysis was performed by associating the burden of the variants defined above within a gene with a phenotype of interest, taking relatedness into account using a mixed model.

In the sex-stratified ExWASs for adult BMI, the authors identified five genes associated with BMI in females (*DIDO1*, *KIAA1109*, *MC4R*, *PTPRG*, and *SLC12A5*) and two genes in males (*MC4R* and *SLTM*). Three of the six genes (*DIDO1*, *PTPRG*, and *SLC12A5*) showed female-specific effects and had not been previously associated with BMI. Additionally, the authors identified six genes (*CALCR*, *INHBE*, *MADD*, *MC4R*, *OBSCN*, and *POMC*) from ExWASs using a recalled childhood adiposity indicator, "comparative size at age 10," which exhibits a strong genetic correlation with childhood BMI and thus can be considered a reliable proxy trait for childhood BMI. Among these, two genes (*MADD* and *OBSCN*) had not been previously associated with childhood adiposity. These findings showcase the presence of rare variants with context-dependent effects on adiposity and demonstrate the potential for additional discoveries by considering these effects. On the other hand, of the eleven genes identified from the sex-stratified and childhood adiposity ExWASs in total, only one gene (*MADD*) appears to be childhood adiposity specific and two genes (*SLC12A5* and *SLTM*) are adult BMI specific. The remaining eight genes show concordant effects between childhood adiposity and adult BMI, although the effects of four genes (*CALCR*, *INHBE*, *MC4R*, and *POMC*) on childhood adiposity tend to be larger than those on adult BMI. These results align with the previous observations that there is a substantial overlap in common variant associations between childhood and adult BMI,[8,9] indicating a strong continuity of childhood adiposity into adulthood.

The authors then sought supporting evidence for their findings by examining common variant associations with BMI from GWASs. Four of the six genes identified from the sex-stratified ExWASs and five of the six genes identified from the childhood adiposity ExWASs were located within 500 kb of GWAS signals. Two genes (*DIDO1* and *MC4R*) from the sex-stratified

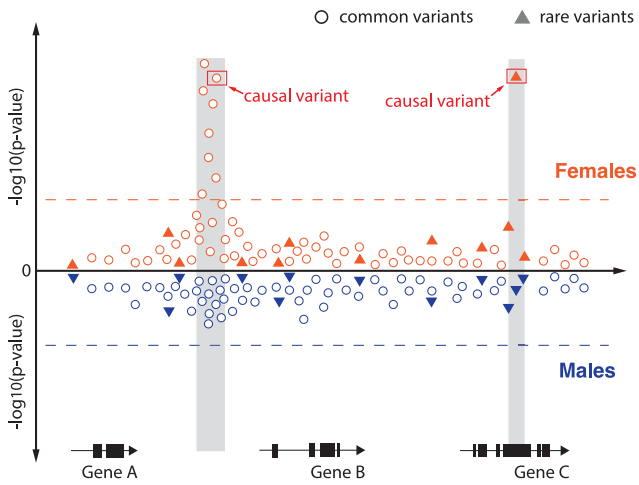

Figure 1. Common and rare variant associations

This schematic diagram depicts the distinction between common and rare variant association analyses in identifying the causal variants and genes. In common variant association analysis, the lead variant is often not causal, whereas in rare variant association analysis, the lead variant is likely to be causal. Furthermore, the diagram underscores the advantage of rare variant association analysis, especially when focusing on damaging variants, in efficiently pinpointing the causal genes associated with the trait of interest.

ExWASs and four genes (*CALCR*, *MADD*, *MC4R*, and *POMC*) from the childhood adiposity ExWASs were supported by gene-level association of common non-synonymous variants with adult BMI. Furthermore, the lead GWAS SNP at the *DIDO1* locus was correlated with known enhancers for *DIDO1* and showed a stronger association with BMI in women compared to men. Colocalization between common variant associations for BMI and *SLTM* expression was also observed. These results suggest a substantial level of convergence of common and rare variant associations. The known functions of the genes identified in the Kaisinger et al. study, along with findings from common variant genome-wide pathway enrichment analyses, imply a potential role of DNA damage response and apoptosis in the susceptibility to obesity throughout the life course. This provides new perspectives on the biological mechanisms underlying obesity.

In conclusion, the study by Kaisinger et al. represents a significant advance in our understanding of the genetic architecture of obesity. The identification of sex- and age-specific genetic effects on obesity highlights the importance of considering these factors in future genetic studies, which can help uncover additional genetic factors contributing to disease susceptibility and improve our understanding of the interplay between genetic and environmental factors in disease development. Although further research is needed to elucidate the precise mechanisms, the implication of DNA damage response and apoptosis pathways in obesity indicates that these biological processes could potentially be targeted for future obesity interventions and therapies. Furthermore, together with previous research,[10] the Kaisinger et al. study underscores the significance of large-scale ExWASs in identifying rare variants and their corresponding genes for complex traits like obesity. As sequencing technologies continue to advance and become more accessible, we can anticipate that additional BMI-associated rare variants and genes will be discovered, which will further enhance our comprehension of the genetic underpinnings of adiposity.

ACKNOWLEDGMENTS

I thank Liyang Song, Ting Qi, and Yazhou Guo for their valuable discussions and assistance in creating the figure. I also thank support received from the "Pioneer" and "Leading Goose" R&D Program of Zhejiang (2022SDXHDX0001), Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (2021R01013), Research Program of Westlake Laboratory of Life Sciences and Biomedicine (202208013), and Research Center for Industries of the Future (RCIF) at Westlake University.

DECLARATION OF INTERESTS

The author declares no competing interests.

REFERENCES

1. Kaisinger, L.R., Kentistou, K.A., Stankovic, S., Gardner, E.J., Day, F.R., Zhao, Y., Mörseburg, A., Carnie, C.J., Zagnoli-Vieira, G., Puddu, F., et al. (2023). Large-scale exome sequence analysis identifies sex- and age-specific determinants of obesity. Cell Genom. *3*, 100362.
2. GBD 2015 Obesity Collaborators, Afshin, A., Forouzanfar, M.H., Reitsma, M.B., Sur, P., Estep, K., Lee, A., Marczak, L., Mokdad, A.H., Moradi-Lakeh, M., et al. (2017). Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N. Engl. J. Med. *377*, 13–27.
3. Locke, A.E., Kahali, B., Berndt, S.I., Justice, A.E., Pers, T.H., Day, F.R., Powell, C., Vedantam, S., Buchkovich, M.L., Yang, J., et al. (2015). Genetic studies of body mass index yield new insights for obesity biology. Nature *518*, 197–206.
4. Yengo, L., Sidorenko, J., Kemper, K.E., Zheng, Z., Wood, A.R., Weedon, M.N., Frayling, T.M., Hirschhorn, J., Yang, J., and Visscher, P.M.; GIANT Consortium (2018). Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. Hum. Mol. Genet. *27*, 3641–3649.
5. Wu, Y., Zheng, Z., Visscher, P.M., and Yang, J. (2017). Quantifying the mapping precision of genome-wide association studies using whole-genome sequencing data. Genome Biol. *18*, 86.
6. Visscher, P.M., Wray, N.R., Zhang, Q., Sklar, P., McCarthy, M.I., Brown, M.A., and Yang, J. (2017). 10 Years of GWAS Discovery: Biology, Function, and Translation. Am. J. Hum. Genet. *101*, 5–22.
7. Cano-Gamez, E., and Trynka, G. (2020). From GWAS to Function: Using Functional Genomics to Identify the Mechanisms Underlying Complex Diseases. Front. Genet. *11*, 424.
8. Bradfield, J.P., Vogelezang, S., Felix, J.F., Chesi, A., Helgeland, Ø., Horikoshi, M., Karhunen, V., Lowry, E., Cousminer, D.L., Ahluwalia, T.S., et al. (2019). A trans-ancestral meta-analysis of genome-wide association studies reveals loci associated with childhood obesity. Hum. Mol. Genet. *28*, 3327–3338.
9. Vogelezang, S., Bradfield, J.P., Ahluwalia, T.S., Curtin, J.A., Lakka, T.A., Grarup, N., Scholz, M., van der Most, P.J., Monnereau, C., Stergiakouli, E., et al. (2020). Novel loci for childhood body mass index and shared heritability with adult cardiometabolic traits. PLoS Genet. *16*, e1008718.
10. Akbari, P., Gilani, A., Sosina, O., Kosmicki, J.A., Khrimian, L., Fang, Y.Y., Persaud, T., Garcia, V., Sun, D., Li, A., et al. (2021). Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. Science *373*, eabf8683.