Review
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Genetics of Type 2 Diabetes Mellitus-Asian Perspective (A Review)

Tip 2 Diabetes Mellitusun Genetiği–Asya Perspektifi (Bir Gözden Geçirme)

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Abstract

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that has come up as a major cause of mortality and continues to cause enormous socio-economic loss across the globe. In the purview of this, a thorough understanding of the pathophysiology, etiology, and pathogenesis of the condition is the need-of-the-hour so as to develop potent therapeutics to have a better control of T2DM. In the developing countries, especially the South Asian region, the condition has become a major health issue owing to the low income and distinct socio-economic patterns. In the European population, a variety of genes have been found to be associated with T2DM; however, their contribution to the other ethnic groups is still unclear. In recent years, various research groups analyzed the prevalence of such genes in Asian populations. The Genome Wide Association Scan (GWAS) successfully identified more than 70 genetic variants that are associated with the T2DM. The present article intends to provide a comprehensive account of the major studies on the genetics of T2DM, with special reference to the Asian population. The various risk factors and the complications associated with the T2DM will be discussed. The review also highlights the major differences and similarities between the susceptibility loci that have been investigated in different ethnicities to provide a novel insight into the disease pathogenesis and its heritability patterns. The information presented, herein, on the genetics of type 2 Diabetes Mellitus holds significance as it paves the way for the development of potential biomarkers and strengthens the fact that specific genetic alterations have important functional roles in the progression or development of T2DM.
Keywords: Diabetes; genetics; genome-wide association scan

Özet

Tip 2 diabetes mellitus (T2DM), dünya genelinde mortalitenin majör nedeni olan bir metabolik bozukluktur. Hastalığın patofizyolojisini, etiyolojisini ve patogenezini daha iyi anlamak için, uygun şekilde odaklanmış terapötik ve araştırma çabaları gereklidir; çünkü hastalığın prevalansı dünya genelinde yaşamları ve ekonomileri etkilemektedir. Gelişmekte olan ülkelerde özellikle Güney Asya bölgesinde, düşük gelir ve farklı sosyoekonomik paternlere bağlı olarak merkezi bir sağlık yükü olmaya başlamaktadır. Avrupalılar arasında gen çeşitliliği T2DM ile ilişkilidir, fakat bu genetik varyantların diğer etnik gruplardaki katkıları hâlâ açık değildir. Asyalılarda yapılan çeşitli yeni çalışmalar bu genlerin bazılarını çoğaltmıştır. "Genom Wide Association Scan (GWAS)", T2DM ile ilişkili 70'ten fazla genetik varyantı başarılı bir şekilde tanımlamıştır. Metodoloji, özellikle Asya ülkelerinde T2DM'nin genetiğiyle ilişkili literatür araştırmasını içermiştir. Bu gözden geçirme T2DM, risk faktörleri ve komplikasyonlarıyla ilişkili majör genetik tabanlı çalışmaların kısa bir özetidir. Ayrıca, farklı etnisitelerde araştırılan duyarlılık lokusunun majör faklılıklarını ve benzerliklerini vurgulamaktadır ki bu da patogenez ve kalıtım mekanizmalarına yeni bir bakış açısı sağlamaktadır. T2DM'nin genetiğinin ortaya çıkarılmasındaki bu ilerlemeler, potansiyel biyomarkerların geliştirilmesinde ve spesifik genetik bozuklukların fonksiyonel rolünün ortadan kaldırılmasında büyük öneme sahiptir.
Anahtar kelimeler: Diyabet; genetik; tüm genom bağlantı analizi

Introduction

Diabetes is a prolonged chronic metabolic disorder that has been regarded as the seventh leading cause of death (1). It is expected that about 642 million individuals will acquire diabetes by the year 2040, as per the 2015 atlas of the International Diabetes Federation (IDF). In the developing countries, like, Pakistan, which has a population of 161.66 million, an estimated 6.7 million people get affected with the condition according to the IDF; this figure is predicted to increase up to 12.8 million by the year 2035 (1, 2). The

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Diabetic Association of Pakistan (DAP) has been involved in conducting national surveys on diabetes and has contributed significantly as the WHO collaborating center for diabetes (3-7).

The rapid increase in the prevalence of diabetes is mainly due to the environmental and behavioral changes that may have resulted from the lifestyle changes. The high rates of urbanization have been recorded for Korea, Malaysia, Singapore, Philippines, and Indonesia, while India, Pakistan, China, and Thailand display intermediate rates followed by Sri Lanka and Bangladesh, where urbanization has been slow. Although, diabetes is caused by various factors, however, a sedentary lifestyle remains the major cause. There has been a high incidence of obesity along with diabetes among obese children and women, especially from the South Asian countries. It has been reported that certain genetic factors are responsible for predisposition of South Asians to diabetes, as confirmed from the data on immigrant Pakistani population that demonstrates the association of certain genetic variants with type 2 diabetes (8). Further, an enormously high rate of chronic complications has been linked to diabetes as the latter affects every organ of the afflicted human body, causing chronic diseases, such as retinopathy, neuropathy, nephropathy, and stroke. The situation gets further complicated by the rising prevalence of metabolic syndrome (MS), childhood obesity, and the younger ages of the onset of type 2 diabetes, which is a common occurrence in the developing world, especially, in the South Asian countries.

In view of this, the present review discusses the relevant studies that have been conducted on the Asian population, in order to highlight the genetic basis of the manifestation of the type 2 DM.

Methodology

At first, information was extracted from the evidence-based research studies on 'genetics of type 2 diabetes' followed by a specific focus on the 'genetics of type 2 diabetes in Asia'. The strategies that were employed to search and retrieve the required information are given below:

A. Retrieval of research evidence on 'genetics of type 2 diabetes'

Database searched for medical research articles

The search for basic research studies on 'genetics of T2D in Asia' was initiated by searching the medical research articles indexed in PubMed. It is managed by the National Library of Medicine (NLM) of the US National Institutes of Health and is the world's largest medical library. PubMed comprises more than 20 million citations for biomedical literature from MEDLINE, life science journals and books that are available online.

Use of citation manager for searching articles

For searching, storing, and sorting the articles, the citation manager software, called the 'Reference Manger' was used. The software was also utilized for citation of the articles in the manuscript form.

Method of retrieving research abstracts from MEDLINE

First and foremost, the abstracts were retrieved from MEDLINE by using the two key words: genetics and type 2 diabetes, together using the Booleans logic operator. The retrieval of all the articles having any of the two terms was ensured by using 'and' in between the terms. In this way, 19105 articles, which were related to 'genetics of type 2 diabetes', were obtained. Another set of articles was retrieved on 'genetics of type 2 diabetes in Asia'; these articles were screened to specifically suit the purpose for writing this review.

Screening of the retrieved articles

The retrieved 19105 articles were screened for the selection of the articles wherein information about 'genetics of type 2 diabetes' was provided. About 1669 articles were filtered that contained data on 'genetics of type 2 diabetes in Asia'. The articles that presented studies on Asian immigrants were also included. The studies, which demonstrated investigations on diabetes in context to other diseases or testing of nutraceuticals or medicines, were excluded. Further, efforts were made to have access to full texts of as many articles as possible.

To include the recent updates on genetic analyses of type 2 diabetes, information from the relevant websites and reports were retrieved by searching for the basic keywords, 'diabetes' and 'Asia' (along with other specific terms) using 'Google'.

Advancement in Genetics of Type 2 Diabetes

The occurrence of T2DM genetic variants differs in various populations and ethnic groups. The identification of these variants among diverse populations has revealed important findings that have contributed toward a better understanding of T2DM at the cellular level. The linkage analysis, candidate gene approach, large-scale association studies, and GWAS have identified more than 70 loci that confer susceptibility to T2DM. Of these, 45 loci were identified in European populations and the other 29 loci were identified in Asian populations, especially, in East and South Asians (Table 1). In order to better understand the pathophysiology of T2DM, immediate benefits were derived from these findings.

Genome Wide Association Scan (*GWAS)*

The two main approaches to understanding such genes are the candidate gene approach and GWAS; however, the latter, which is able to simultaneously scan several loci in any population, is less expensive and less error-prone (9). GWAS revealed the association of multiple loci with T2DM in geographically different populations, such as Americans, Caucasians, Australians, West Africans and Europeans (10-14).

The GWAS studies, on a larger scale, have helped us to investigate the genetic basis of the disease and identified dozens of variants that are associated with the T2DM. However, certain rare variants often remain undetected due to the limitations in genotyping arrays. Still, the best method to detect and identify novel genes in diverse populations remains the GWAS, as it provides more elaborate information on the genetic architecture of disease pathophysiology (15-18).

Although GWAS has greatly improved our understanding towards the genetic basis of T2D, the current genetic risk models for T2D cannot be applied to all populations because most of these studies have been performed in the Europeans. Only limited research studies have been conducted in the South Asians. The discovery of

Table 1. Type2 diabetes susceptibility genes/loci identified in Asian region.

Reference number	Gene/Locus	Gene name	Probable mechanism	Region of gene identified
19,29,42	PPARG	Peroxisome proliferative activated receptor gamma gene	Insulin action	European
19	KCNJ11	Potassium inwardly-rectifying channel, subfamily J, member 11	Beta cell function	European/Asian
19,20,25,29	TCF7L2	Transcription factor 7 like 2	Beta cell function	European/Asian
19,20	CDKAL1	CDK5 regulatory subunit associated protein 1-like 1	Beta cell function	European/Asian
19,20,42	CDKN2A/B	Cyclin-dependent kinase inhibitor-2A/2B	Beta cell function	European/Asian
19,20,29	IGF2BP2	Insulin-like growth factor 2 binding protein 2	Beta cell function	European/Asian
19,20,42	HHEX/IDE	Hematopoietically expressed Homeobox- insulin-degrading enzyme	Beta cell function	European/Asian
19,26,28,29,42	FTO	Fat mass and obesity-associated protein	Obesity	European/Asian
19,26,41,42	SLC30A8	Solute carrier family 30, member 8	Beta cell function	European/Asian
20,23,42	KCNQ1	Potassium voltage-gated channel subfamily KQT member 1	Beta cell function	European/Asian
22,40	MNTR1B	Melatonin receptor type 1B	Beta cell function	European/Asian
49	HNF1beta	Hepatocyte nuclear factor 1-beta (Transcription factor 2)	Beta cell function	European
37	ST6GAL1	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	Beta cell function	Asian
37	GRB14	Growth Factor Receptor-Bound Protein 14	Insulin	Asian
37	HMG20A	High mobility protein 20 A	Unknown	Asian
37	VPS26A	Vacuolar Protein Sorting 26 Homolog A	Unknown	Asian
37	HNF4A	Hepatocyte Nuclear Factor 4, Alpha	Beta cell function	Asian
37	AP3S2	Adaptor-Related Protein Complex 3, Sigma 2 Subunit	Unknown	Asian
38	CDC123/CAMKID	Cell division cycle 123 homolog (S. cerevisiae)/calcium/ Calmodulin dependent protein kinase ID	Beta cell function	Asian/European
38	THADA	Thyroid adenoma associated	Beta cell function	Asian/European
38	NOTCH2	Neurogenic locus notch homolog protein 2	Unknown	Asian/European
38	TSPAN8/LGRS	Tetraspanin8/Leucine-rich repeat containing G protein-coupled receptor 5	Beta cell function	Asian/European
38,42	JAZF1	Juxta-posed with another zinc finger gene 1	Beta cell function	European/Asian
38	ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif, 9	Decreased insulin sensitivity	European
40	GCKR	Glucokinase regulatory protein	Increased insulin resistance	Asian
40	GCK	Glucokinase	Beta cell function	Asian
40	G6PC2	Glucose-6-phosphatase, catalytic, 2	Beta cell function	Asian
41	ADCY5	Adenylate cyclase 5	Insulin action	Asian
41	GLIS3	GLIS Family Zinc Finger 3	Beta cell function	Asian
42	IRS1	Insulin Receptor Substrate 1	Increased insulin resistance	European/Asian
42	CHCHD9	Putative coiled-coil-helix-coiledcoil-helix domain-containing protein CHCHD2P9	Unknown	European/Asian
42	DUSP9	Dual specificity phosphatase 9	Phospatase	European/Asian
42	KLF14	Kruppel-Like Factor 14	Insulin action	European/Asian
44,45	RAGE	Receptor for Advanced Glycation End-products	Insulin action	Asian
44,45	PAI-1	Plasminogen activator inhibitor-1	Insulin action	Asian
49	HMGA2	High Mobility Group AT-Hook 2	Transcriptional regulator	African-American
49	BCL2	B-cell lymphoma-2	Beta cell function	African-American
50	VPS13C/	Vacuolar Protein Sorting 13 Homolog C	Beta cell function	European
50	C2CD4A/B	C2 Calcium-Dependent Domain Containing 4A	Beta cell function	European
50	ARAP1	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 1	Insulin action	European
51,52	GSTMI	Glutathione-S-transferase M1	Insulin action	Asian
51,52	GSTP1	Glutathione S-Transferase Pi 1	Insulin action	Asian
51,52	GSTT1	Glutathione S-transferase theta 1	Insulin action	Asian
54	IL-10	Interleukin 10	Insulin sensitivity	Asian/Mid-Eastern
55	ARHGEF11	Rho Guanine Nucleotide Exchange Factor (GEF) 11	Insulin action	Pima indians
56	SLC16A11	Solute carrier family 16 member 11	Unknown	Mexican/American

new loci in different populations is subject to inter-population differences in the allele frequencies and effect sizes. There is growing evidence that the Asian-Indians are at a higher risk for T2D as compared to the other populations. Over the years, multiple genes have been successfully identified that contribute to T2D susceptibility. The approaches used include linkage analysis, candidate gene approach, large-scale association studies, and genome-wide association studies (GWAS). In an attempt to minimize the T2DM burden, a combined analysis of these loci, such as the construction of genetic risk scores, has to be done for easier and early diagnosis and development of preventive strategies against T2DM.

Genetics of type 2 diabetes in East Asian population

As described above, the genetic studies of T2DM in European populations have enormously contributed to our understanding of T2DM susceptibility. However, the existing literature only provides a partial explanation for the heritability of T2DM. It is well known that the discrepancies exist in the allelic frequencies and the effect size in different ethnic groups. It is, therefore, important to understand whether such genetic variations are also applicable to the other ethnic populations.

Several research groups increased the number of confirmed T2DM susceptibility loci to nine (PPAR , KCNJ11, TCF7L2, CDKAL1, CDKN2A/B, IGF2BP2, HHEX/IDE, FTO, and SLC30A8), all these genes may be responsible for affecting the -cell function, except for the PPAR and FTO, which mainly affects the insulin sensitivity (19, 20). The studies from China, Denmark and few Asian countries revealed that a significant association exists between CDKN2A/2B, SLC30A8, CDKAL1 and KCNQ1 gene polymorphisms with T2DM. A number of GWA studies identified KCNJ11 and TCF7L2 genes as the susceptibility genes for T2DM in Japanese and Chinese populations, respectively. Similarly, previously reported genes from the European population, including the IGF2BP2, HHEX, SLC30A8, CDKAL1 and CDKN2A-2B have been detected in populations of Japan, Hong Kong and Korea, of which only CDKAL1 and CDKN2A-2B genes show association with the T2DM in Chinese population (21). Prokopenko and colleagues reported that the variants in MTNR1B, influence fasting glucose levels in European population (22). Likewise, KCNQ1 gene has been detected in Chinese population (23); however, IGF2BP2 was not identified as the diabetes susceptibility loci in the latter (24). In comparison to the East Asians, the frequency of genetic variation in TCF7L2 gene has been reportedly higher in Caucasians, Africans and Indians (25). Significant but weak association of FTO variants, on both BMI and T2DM, in East Asian population was identified (26).

Genetics of type 2 diabetes in South Asian population

As compared to Europeans, South Asians have approximately six times high risk of T2DM, as reported in the meta-analysis, which includes the 'disease-association studies' (27). A study, involving approximately 41,000 Europeans, showed that the FTO gene polymorphism has significant effects on obesity-related measures and T2DM, as accounted by body mass index (BMI) (28). On the contrary, only a few studies have been reported from the South Asia to highlight the association of FTO gene variants with T2DM and obesity. A study on Sikh population from the Northern India observed the influence of ProAla, IGF2BP2, TCLF7L2, and FTO gene variants on adiposity and T2DM (29). Several research studies confirmed FTO as the T2DM susceptibility locus independent of BMI. Further studies among the South Asian population are required to validate these findings (30).

It has been reported that every 10/100 United Kingdom (UK) based South Asians suffers from T2DM (31). In spite of a high prevalence rate of T2DM in the above population, data on the genetic basis of the diseases remains scarce in it. Investigation of genetic variants in the TCF7L2 gene in two South Asian cohorts contributes to the recent efforts in genomics that led to the investigation of potential T2DM susceptibility loci. The two sets of the South Asian population include residents of UK and the Western India; the SNPs investigated were rs7903146 and rs12255372 (32, 33). Two recent studies reported a significant association of TCF7L2 with T2DM while assessing the disease burden in the Indian population (33, 34).

Furthermore, two separate studies failed to show any significant association of the Pro12Ala with T2DM in South Indian population of Chennai or in Singapore population. ProAla polymorphism has been reportedly protective against diabetes in Caucasians (35, 36).

A multi-centered study, which was conducted in the South Asian individuals in London, Pakistan, and Singapore, revealed the association of six genetic variants at various cytogenetic locations (ST6GAL1, GRB14, HMG20A, VPS26A, HNF4 and AP3S2). Furthermore, ST6GAL1, GRB14 and HNF4A polymorphisms were also associated with impaired insulin sensitivity and altered ß-cell function (37). Recently, a meta-analysis of three GWA studies identified six loci (CDC123/CAMKID, THADA, NOTCH2, TSPAN8/LGRS, JAZF1, and ADAMTS9) in Khatri Sikhs in relation to T2DM. The authors observed an association of the only CDC123/CAMKID with T2DM under a dominant model. Moreover, the effect of risk allele associated with this gene was found to be linked with altered ß-cell function (38).

During T2DM, the FTO expression increases in the muscle that further alters insulin signaling, enhances lipogenesis and ROS production, and also induces mitochondrial dysfunction (39). Another Indian study reported the association of MTNR1B, GCKR, GCK, and G6PC2 gene polymorphisms with abnormal plasma glucose levels as a risk of T2DM and the related metabolic disorders in Asian Indians (40).

The studies conducted on Pakistani population have predicted association of TCF7L2 and SLC30A8, ADCY5 and GLIS3 polymorphisms with T2DM (41). Similarly, recent GWA study investigated around thirty SNPs in two Punjabi populations of Mirpur, Pakistan. The two different populations comprised residents of Azad Kashmir and UK. SNPs within the TCF7L2, PPARG, CDKN2A/2B, FTO, IGF2BP2, HHEX/IDE, KCNQ1, SLC30A8, IRS1, JAZF1, CHCHD9, DUSP9 and KLF14 genes were found to be associated with T2DM (42).

A study conducted in Vietnam reported that the FTO genetic variants are associated with T2DM even after adjustment for age, sex, systolic blood pressure, socioeconomic status, lifestyle factors and obesity-related traits. As per the study, the risk associated with each risk allele of rs 9939609, was 1.80-1.92 (43).

The variants of RAGE and PAI-1 genes have been shown to be linked with micro- and macro-vascular complications in Caucasians (44, 45). Another study indicated an association of RAGE

and GFPT2 gene polymorphisms with diabetic nephropathy in Indian subjects (46). Similarly, the RAGE polymorphism has been reported to influence diabetic nephropathy, with one of its alleles exhibiting a protective effect against macrovascular complications of diabetes (47). Similarly, a meta-analysis of eight studies showed the protective effect of Pro12Ala polymorphism against retinopathy. A significant association of Ala allele with retinopathy in Caucasians was observed; however, o significant results were observed in association with T2DM and the other related complications. No association of the C677T polymorphism of MTHFR gene was found in Africans, Asians, and Caucasians (48). MTHFR is a gene that is involved in DNA methylation and synthesis along with the regulation of folate activity. It has been reported that the mutant homozygote and heterozygote of C677T polymorphism of MTHFR increases plasma homocysteine that is an important factor leading to diabetic nephropathy (DN).

Genes associated with type 2 diabetes in non-Asian populations

With the advent of GWAS, the dissection of the genetic basis for susceptibility to T2D has experienced major breakthroughs in the other parts of the world as well.

Grant and colleagues reported the association of TCF7L2 gene variants with T2DM in populations of Denmark, Iceland and United States of America (USA). Moreover, HMGA2 and BCL2 genes were also identified as T2DM risk loci in African-Americans and the other multi-ethnic groups, respectively. The study also analyzed the effect of risk alleles of T2DM susceptibility loci in African-Americans, Hispanics, and Asians (49). Previously, genes including TCF7L2, SLC30A8, VPS13C/C2CD4A/B, and ARAP1 have been reported as T2DM susceptibility loci in ancestral Europeans (50). The association between different genes and T2DM has been assessed by systematic reviews and meta-analysis studies. Glutathione-S-transferase including the GSTMI, GSTT1, and GSTP1 are important genes and their association with diabetes has been investigated in two meta-analysis studies (51, 52). Glutathione S-transferase M1 (*GSTM1*) and glutathione S-transferase T1 (*GSTT1*) genes are polymorphic in humans and the null genotypes render the enzymes inactive. Several studies assessed the associations between *GSTM1/GSTT1* null genotypes and DM risk but demonstrated conflicting results (53), while no significant association was found between GSTP1 and diabetes (51). Further, 1082A/G polymorphism of IL-10 seems to be a risk factor for T2DM in Asians, but not in Europeans or Africans (54).

Among the candidate genes that are related to T2DM, the TCF7L2 exhibits one of the strongest genetic associations with diabetes. In a meta-analysis study after pooling all the data of European, African, and Asian populations, it has been revealed that rs12255372 polymorphism of the TCF7L2 gene, significantly increases the risk of T2DM. In line with such findings, a positive association is observed between rs12255372 and rs7903146 variants of TCF7L2 gene and T2DM in Iranian population (54).

Another study reported that 1082GG genotype of IL-10 and 174CC genotype of IL-6 are potential risk factors for T2DM in Egyptians (55). The findings from Pima Indian population suggested that the increased risk of type 2 diabetes was due to the variation within ARHGEF11 gene, which is nominally associated with increased insulin resistance (56). SLC16A11 is identified as a novel candidate gene for type 2 diabetes with a possible role in triacylglycerol metabolism in Mexican and Latin American population (57). The Pro12Ala polymorphism of PPAR was recorded as a protective variant, especially in the Asian population, although the results were highly heterogeneous (58).

It should be noted that the known variants cover only a minuscule amount of the overall estimated genetic heritability; therefore, the complete understanding of the pathogenesis of type 2 diabetes still requires a lot of efforts.

Conclusion

Several studies specify that diabetes is a heterogeneous disease. For the discovery of the other genetic susceptibility loci and to further clarify the unclear heritability pattern associated with these complex diseases, investigators should follow the genome-wide approaches, such as GWAS. Employing the techniques for *TCF7L2* and *FTO,* to elucidate the underlying genetic variations, will be crucial for the identification of specific targets for future therapeutic interventions. The contradictory results might be due to the generation of insufficient data; therefore, a more comprehensive approach is suggested for GWAS on specified populations with large sample size.

However, as the disease is multifactorial in nature, the effects of identified genes and pathways on T2D still remain largely unknown. The identification of prognostic and predictive biomarkers seems crucial to understanding the pathogenesis of T2D, as well as the novel therapeutic targets, which in turn should lead to improved outcomes in the affected patients. In contrast to the previous studies, it has been proposed that accumulation of rare variants with mild deleterious effects may substantially increase the relative risk at the individual level. Indeed, with the next generation of sequencing technologies, rare variants may be identified. Such results, together with the known common susceptibility variants, may increase the discriminative value of genetic risk factors and push the limit towards a threshold that may be acceptable for clinical utility.

Ethics

Ethical approval was taken from the Institutional Review Board (IRB) of BIDE.

Authorship Contributions

Concept: Asher Fawwad and Abdul Basit, Design: Asher Fawwad and Abdul Basit, Data Collection or Processing: Asher Fawwad, Analysis or Interpretation: Asher Fawwad and Rashid Kanza, Literature Search: Rashid Kanza and Asher Fawwad, Writing: Rashid Kanza and Asher Fawwad.

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