



Article review: MCPS and *snipar*

B.Sc. ROBERTO OLVERA-HERNANDEZ

*Centre for Genomic Sciences (CCG),
National Autonomous University of Mexico (UNAM)*

February 22, 2025



1. Mexico City Prospective Study (MCPS)

1.1 Recruitment and baseline data

1.2 Genetic overview

1.3 Population structure and ancestry

2. Mendelian Imputation

2.1 Family Genome-Wide Association Studies (FGWAS)

1 Mexico City Prospective Study (MCPS)

1 Mexico City Prospective Study (MCPS)

1.1 Recruitment and baseline data



Overview

Over **150,000 participants** were recruited in two districts between **1998 and 2004**.

- ▶ Baseline questionnaire.
- ▶ Blood samples.
- ▶ Physical measurements.
- ▶ Linkage to mortality.

COHORT PROFILE

Cohort Profile: The Mexico City Prospective Study

Roberto Tapia-Conyer,¹ Pablo Kuri-Morales,² Jesús Alegre-Díaz,² Gary Whitlock,^{3*}
Jonathan Emberson,³ Sarah Clark,³ Richard Peto³ and Rory Collins³



Figure 1: Map showing the location of the MCPS districts (Tapia-Conyer et al. 2006, *International Journal of Epidemiology*).



Baseline data

Socio-demographic

- ▶ Age and sex
- ▶ Area of residence
- ▶ Marital status
- ▶ Educational achievement
- ▶ Occupation
- ▶ Income
- ▶ Health service provider



Baseline data

Socio-demographic

- ▶ Age and sex
- ▶ Area of residence
- ▶ Marital status
- ▶ Educational achievement
- ▶ Occupation
- ▶ Income
- ▶ Health service provider

Lifestyle characteristics

- ▶ Diet (fruit/vegetables, fried food, types of oil)
- ▶ Smoking and alcohol
- ▶ Physical activity
- ▶ Sleep duration



Baseline data

Socio-demographic

- ▶ Age and sex
- ▶ Area of residence
- ▶ Marital status
- ▶ Educational achievement
- ▶ Occupation
- ▶ Income
- ▶ Health service provider

Reproductive history (women)

- ▶ Menopausal status
- ▶ Hysterectomy
- ▶ Oopherectomy
- ▶ HRT
- ▶ Contraceptive use
- ▶ Pregnancy (age and number)

Lifestyle characteristics

- ▶ Diet (fruit/vegetables, fried food, types of oil)
- ▶ Smoking and alcohol
- ▶ Physical activity
- ▶ Sleep duration



Baseline data

Socio-demographic

- ▶ Age and sex
- ▶ Area of residence
- ▶ Marital status
- ▶ Educational achievement
- ▶ Occupation
- ▶ Income
- ▶ Health service provider

Reproductive history (women)

- ▶ Menopausal status
- ▶ Hysterectomy
- ▶ Oopherectomy
- ▶ HRT
- ▶ Contraceptive use
- ▶ Pregnancy (age and number)

Lifestyle characteristics

- ▶ Diet (fruit/vegetables, fried food, types of oil)
- ▶ Smoking and alcohol
- ▶ Physical activity
- ▶ Sleep duration

Physical measurements

- ▶ Height
- ▶ Weight
- ▶ Waist and hip circumference
- ▶ Systolic and diastolic blood pressure



Baseline data

Socio-demographic

- ▶ Age and sex
- ▶ Area of residence
- ▶ Marital status
- ▶ Educational achievement
- ▶ Occupation
- ▶ Income
- ▶ Health service provider

Reproductive history (women)

- ▶ Menopausal status
- ▶ Hysterectomy
- ▶ Oopherectomy
- ▶ HRT
- ▶ Contraceptive use
- ▶ Pregnancy (age and number)

Blood samples

- ▶ Plasma & buffy coat
- ▶ HbA1c and other essays
- ▶ NMR metabolomics (e.g. fatty acids, cholines, lipoprotein subclasses, etc.)

Lifestyle characteristics

- ▶ Diet (fruit/vegetables, fried food, types of oil)
- ▶ Smoking and alcohol
- ▶ Physical activity
- ▶ Sleep duration

Physical measurements

- ▶ Height
- ▶ Weight
- ▶ Waist and hip circumference
- ▶ Systolic and diastolic blood pressure



Baseline data

Socio-demographic

- ▶ Age and sex
- ▶ Area of residence
- ▶ Marital status
- ▶ Educational achievement
- ▶ Occupation
- ▶ Income
- ▶ Health service provider

Reproductive history (women)

- ▶ Menopausal status
- ▶ Hysterectomy
- ▶ Oopherectomy
- ▶ HRT
- ▶ Contraceptive use
- ▶ Pregnancy (age and number)

Blood samples

- ▶ Plasma & buffy coat
- ▶ HbA1c and other essays
- ▶ NMR metabolomics (e.g. fatty acids, cholines, lipoprotein subclasses, etc.)

Lifestyle characteristics

- ▶ Diet (fruit/vegetables, fried food, types of oil)
- ▶ Smoking and alcohol
- ▶ Physical activity
- ▶ Sleep duration

Physical measurements

- ▶ Height
- ▶ Weight
- ▶ Waist and hip circumference
- ▶ Systolic and diastolic blood pressure

Prior diseases and medications

Participants were asked if they had ever been diagnosed with any of the listed diseases (binary: Yes or No).

1 Mexico City Prospective Study (MCPS)

1.2 Genetic overview



Genetic datasets

- ▶ Genetic datasets were added later by Ziyatdinov et al. (2023), making it one of the **largest** studies for **non-eurpean** populations.



Genetic datasets

- ▶ Genetic datasets were added later by Ziyatdinov et al. (2023), making it one of the **largest** studies for **non-eurpean** populations.
- ▶ Comparison (WES and WGS) were made with other datasets: **UK Biobank, TOPMed, gnomAD**.



Genetic datasets

- ▶ Genetic datasets were added later by Ziyatdinov et al. (2023), making it one of the **largest** studies for **non-eurpean** populations.
- ▶ Comparison (WES and WGS) were made with other datasets: **UK Biobank, TOPMed, gnomAD**.

Genome-Wide Genotyping

- ▶ Illumina — GSAv2 chip array
- ▶ 138,511 individuals



Genetic datasets

- ▶ Genetic datasets were added later by Ziyatdinov et al. (2023), making it one of the **largest** studies for **non-eurpean** populations.
- ▶ Comparison (WES and WGS) were made with other datasets: **UK Biobank, TOPMed, gnomAD**.

Genome-Wide Genotyping

- ▶ Illumina — GSAv2 chip array
- ▶ 138,511 individuals

Exome Sequencing (WES)

- ▶ $n = 141,046$ individuals
- Variants:**
- ▶ *Total*: 9.3 million.
 - ▶ *Coding regions*: 4.0 million in 19,110 genes.
 - ▶ *Unique MCPS*: 1.4 million.



Genetic datasets

- ▶ Genetic datasets were added later by Ziyatdinov et al. (2023), making it one of the **largest** studies for **non-eurpean** populations.
- ▶ Comparison (WES and WGS) were made with other datasets: **UK Biobank, TOPMed, gnomAD**.

Genome-Wide Genotyping

- ▶ Illumina — GSAv2 chip array
- ▶ 138,511 individuals

Exome Sequencing (WES)

- ▶ $n = 141,046$ individuals
- Variants:**
- ▶ *Total*: 9.3 million.
 - ▶ *Coding regions*: 4.0 million in 19,110 genes.
 - ▶ *Unique MCPS*: 1.4 million.

Whole-Genome Sequencing (WGS)

- ▶ $n = 9,950$ individuals
- Variants:**
- ▶ *Total*: 131.9 million.
 - ▶ *Coding regions*: 1.5 million.
 - ▶ *Unique MCPS*: 31.5 million.



Genetic datasets

- ▶ Genetic datasets were added later by Ziyatdinov et al. (2023), making it one of the **largest** studies for **non-eurpean** populations.
- ▶ Comparison (WES and WGS) were made with other datasets: **UK Biobank, TOPMed, gnomAD**.

Genome-Wide Genotyping

- ▶ Illumina — GSAv2 chip array
- ▶ 138,511 individuals

Exome Sequencing (WES)

- ▶ $n = 141,046$ individuals
- Variants:**
- ▶ *Total*: 9.3 million.
 - ▶ *Coding regions*: 4.0 million in 19,110 genes.
 - ▶ *Unique MCPS*: 1.4 million.

Whole-Genome Sequencing (WGS)

- ▶ $n = 9,950$ individuals
- Variants:**
- ▶ *Total*: 131.9 million.
 - ▶ *Coding regions*: 1.5 million.
 - ▶ *Unique MCPS*: 31.5 million.

- ▶ Both **WES** and **WGS** share **93.2%** of the variants, with an increment of **2.3%** on **WGS** data.



WES and WGS - Comparisons

- ▶ Lower proportion of **singletons**, indicates *extensive familial relatedness*.
- ▶ Increased number of **predicted loss of function (pLOF)** variants.

Variant Type	MAF	MCPS Freeze 150 WES All ancestries		UKB WES All ancestries (N=454,787)	TOPMed Freeze 8 ^a All ancestries (N=132,345)	gnomAD 3.1 ^a All ancestries (N=76,156)
		Total Variants	Unique to MCPS			
All coding ^b	All	3,993,480	1,378,929	12,251,048	7,967,776	6,720,277
	Singleton	1,232,799	641,245	5,745,376	3,629,356	3,487,928
	Doubleton - 0.01%	2,249,180	718,941	6,105,074	3,755,427	2,619,225
	0.01-0.1%	378,837	18,651	300,716	384,065	397,323
	0.1-1%	81,522	46	54,860	118,746	129,469
	1-5%	17,083	8	17,318	39,559	41,791
	>5%	34,059	38	27,704	40,623	44,541



WES and WGS - Comparisons

- ▶ Lower proportion of **singletons**, indicates *extensive familial relatedness*.
- ▶ Increased number of **predicted loss of function (pLOF)** variants.

Variant Type	MAF	MCPS WGS All ancestries (N=9950)		TOPMed Freeze 8 ^a All ancestries (N=132,345)	gnomAD 3.1 ^a All ancestries (N=76,156)
		Total Variants	Unique to MCPS		
All Variants	All	131,851,585	31,533,601	705,482,499	643,434,862
	Singleton	57,885,022	23,866,451	323,651,578	317,422,028
	Doubleton-0.1%	54,213,931	7,621,741	354,185,173	287,971,390
	0.1-1%	10,811,295	33,835	14,418,471	20,236,181
	1-5%	2,635,764	4,868	5,928,971	8,153,113
	>5%	6,305,573	6,706	7,298,306	9,652,150



Family networks

Estimation

Relatedness was estimated through *identity-by-descent (IBD)* sharing.



Family networks

Estimation

Relatedness was estimated through *identity-by-descent (IBD)* sharing.

About 71% of individuals have **at least one relative** present in the MCPS dataset.

- ▶ **Parent-Offspring (PO):** 31,597 relationships.
- ▶ **Sibling Pairs (FS):** 29,482 relationships.
- ▶ **Second Degree (2nd):** 47,080 relationships.
- ▶ **Third Degree (3rd):** 120,180 relationships.



Family networks

Estimation

Relatedness was estimated through *identity-by-descent (IBD)* sharing.

About 71% of individuals have **at least one relative** present in the MCPS dataset.

- ▶ **Parent-Offspring (PO):** 31,597 relationships.
- ▶ **Sibling Pairs (FS):** 29,482 relationships.
- ▶ **Second Degree (2nd):** 47,080 relationships.
- ▶ **Third Degree (3rd):** 120,180 relationships.

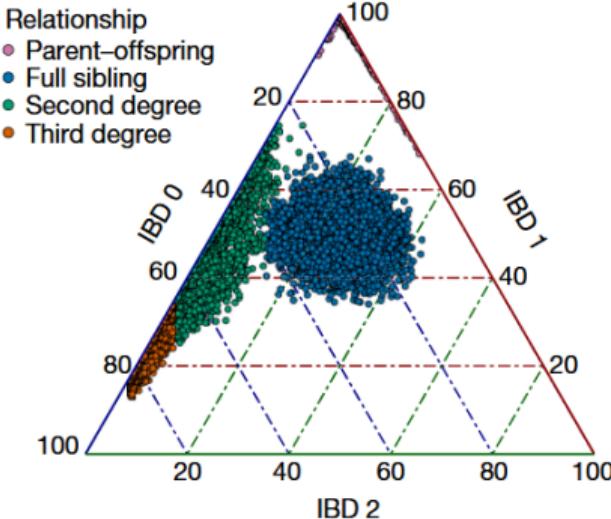
a

Figure 2: Percentage of genome estimated to have zero, one or two IBD alleles (Ziyatdinov et al. 2023, *Nature*).



Family networks

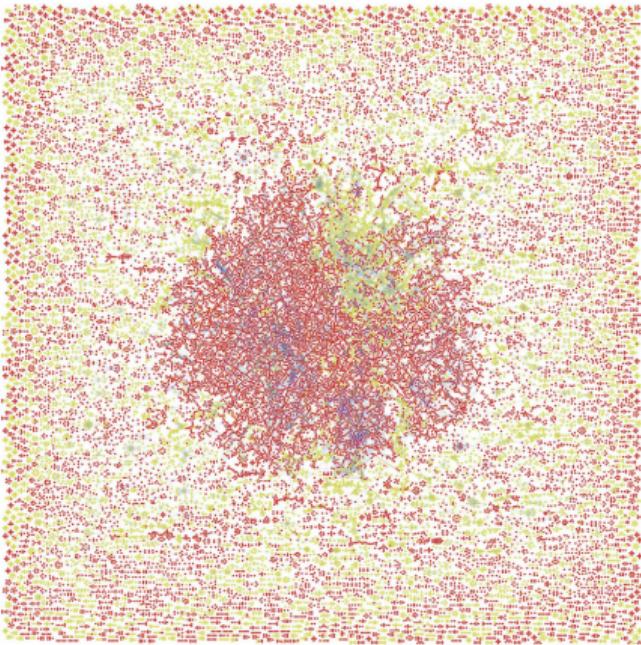


Figure 3: Graph of second-degree family networks of size four or greater (Ziyatdinov et al. 2023, *Nature*).



Family networks

The levels of *relatedness* were:

- ▶ much higher than those from the **UK Biobank (UKB)**.
- ▶ comparable with the **Geisinger Health Study (GHS)**—both MCPS and GHS recruited in *close proximity*.

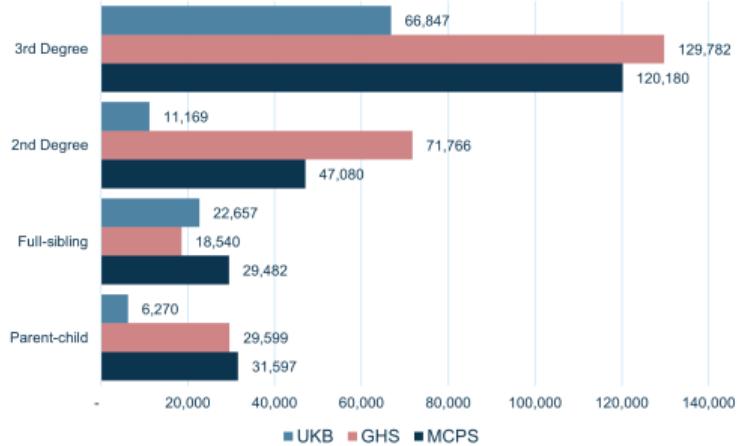


Figure 4: Comparison of network sizes in MCPS, UKB and GHS. Data extracted from Supplementary Table 25 (Ziyatdinov et al. 2023, *Nature*).

1 Mexico City Prospective Study (MCPS)

1.3 Population structure and ancestry



Admixture characterization (PCA)

- ▶ 1,000 Genomes Project (1KG): 108 African (Yoruba); 107 European (Iberian).
- ▶ Metabolic Analysis of an Indigenous Samples (MAIS)¹: 591 Indigenous Mexican (north, northwest, central, south, southeast).

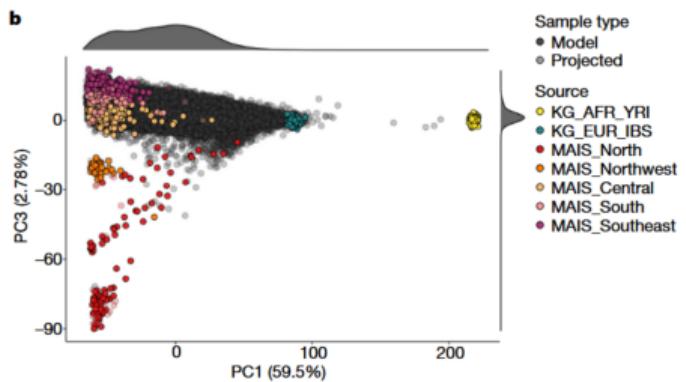


Figure 5: *Model one*: projection of 500 MCPS unrelated samples (Ziyatdinov et al. 2023, *Nature*).

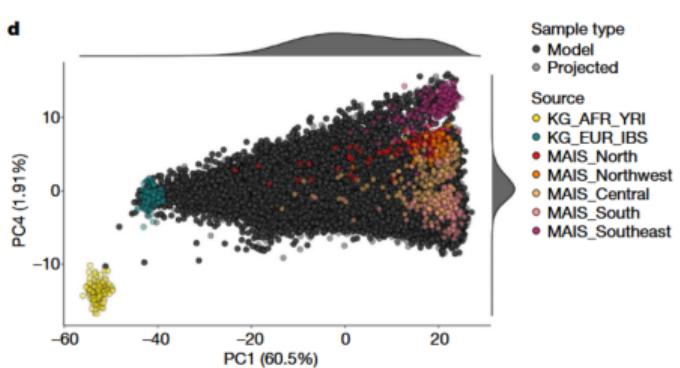


Figure 6: *Model two*: projection of 58,051 MCPS unrelated samples (Ziyatdinov et al. 2023, *Nature*).

¹García-Ortiz et al. 2021, *Nature Communications*



Discrete admixture characterization

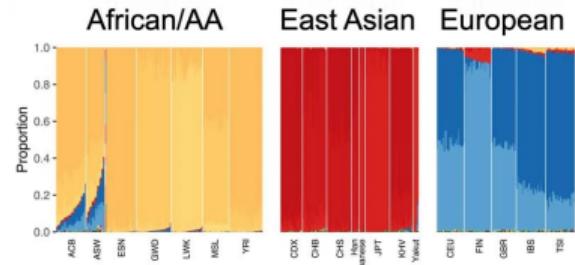


Figure 7: Ancestry proportion estimates for 137,511 MCPS samples. Datasets: 1KG, HGDP, and MAIS datasets are shown (Ziyatdinov et al. 2023, *Nature*).



Discrete admixture characterization

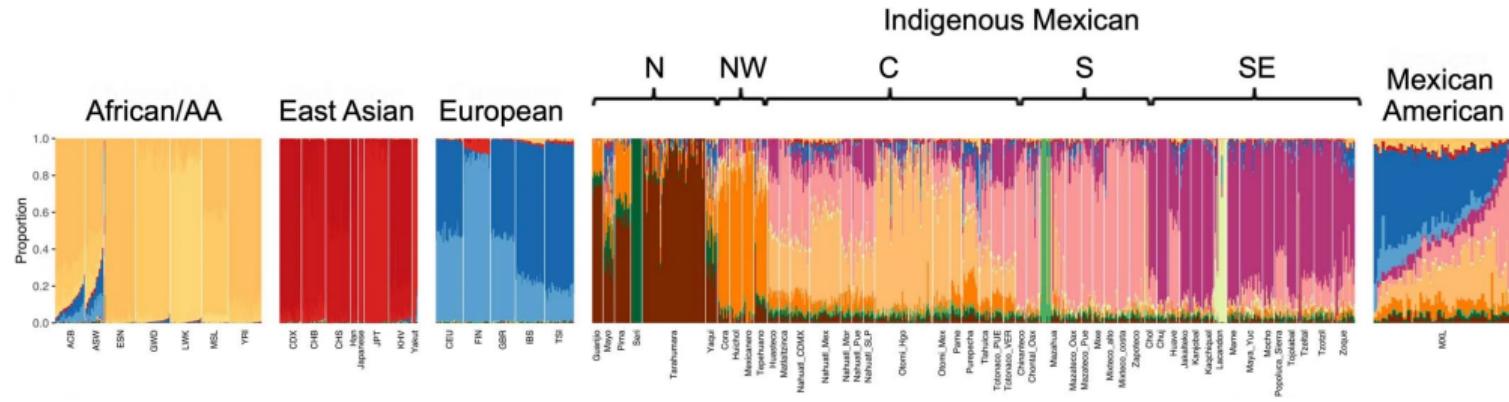


Figure 7: Ancestry proportion estimates for 137,511 MCPS samples. Datasets: 1KG, HGDP, and MAIS datasets are shown (Ziyatdinov et al. 2023, *Nature*).



Discrete admixture characterization

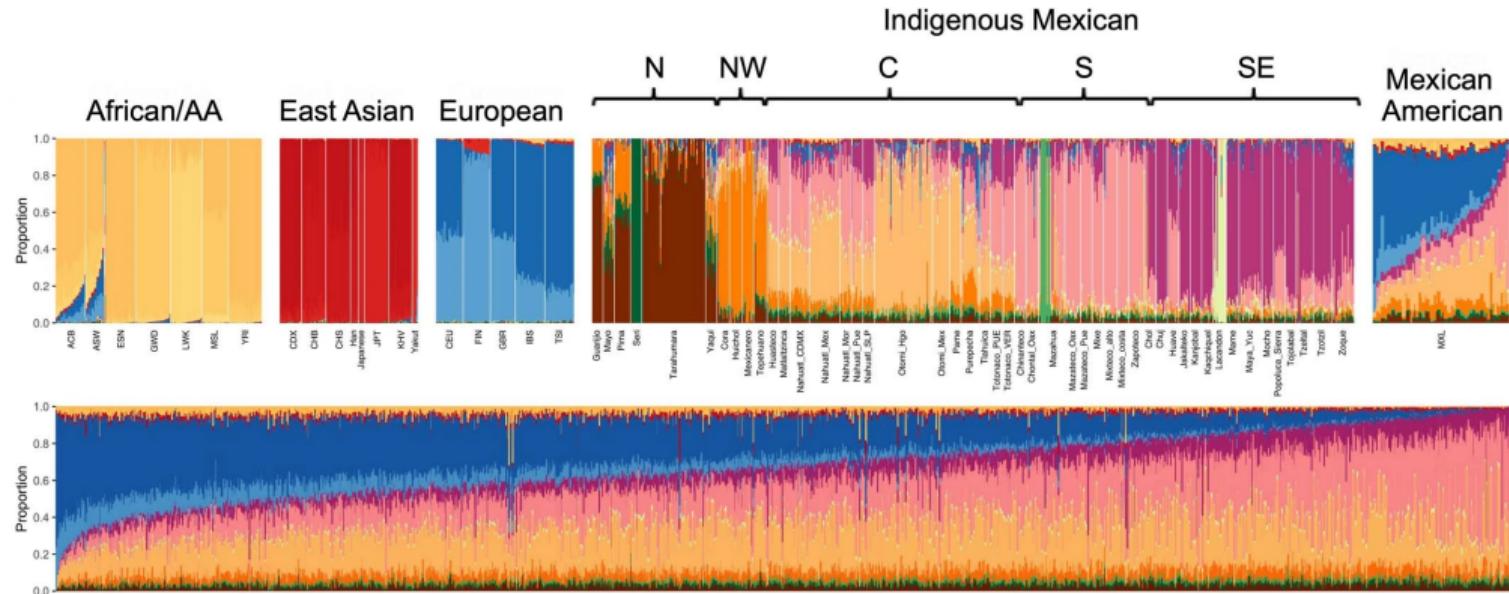


Figure 7: Ancestry proportion estimates for 137,511 MCPS samples. Datasets: 1KG, HGDP, and MAIS datasets are shown (Ziyatdinov et al. 2023, *Nature*).

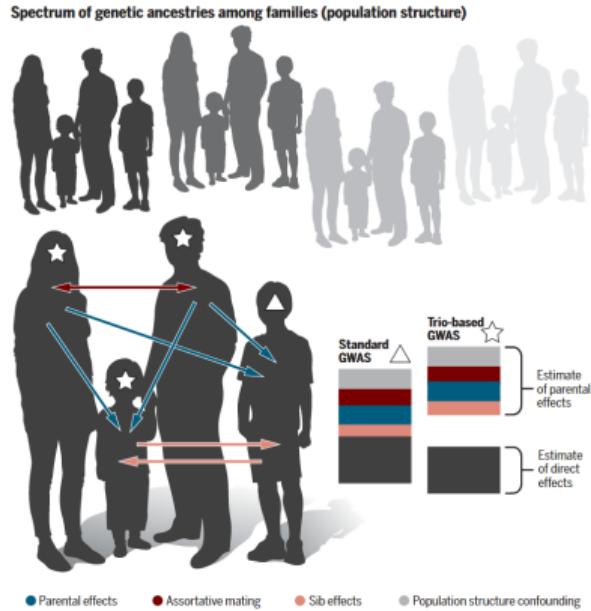
2 Mendelian Imputation

2 Mendelian Imputation

2.1 Family Genome-Wide Association Studies (FGWAS)



Why use them?



^aDirect Genetic Effects

Figure 8: Signals captured by FGWAS in families
(Young et al. 2019, *Science*).



Why use them?

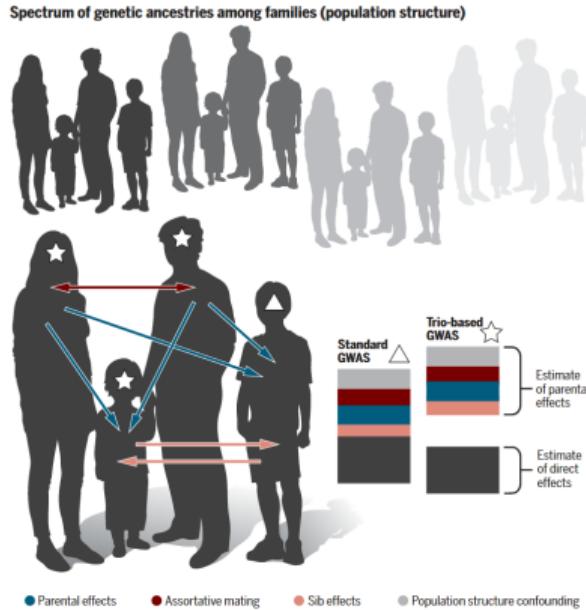


Figure 8: Signals captured by FGWAS in families
(Young et al. 2019, *Science*).

Unbiased GWAS

- ▶ Can discriminate **DGEs^a** and **Population Effects** using **parental genotypes** as controls.

^aDirect Genetic Effects



Why use them?

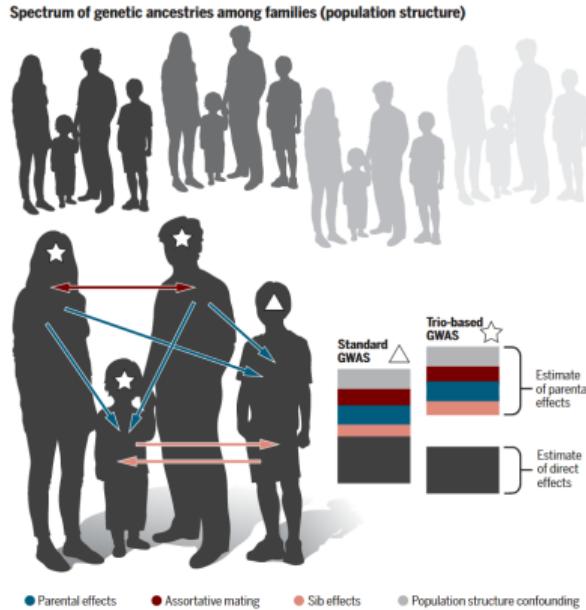


Figure 8: Signals captured by FGWAS in families
(Young et al. 2019, *Science*).

Unbiased GWAS

- ▶ Can discriminate **DGEs^a** and **Population Effects** using **parental genotypes** as controls.
- ▶ Source of genetic variation is *within-family*.

^aDirect Genetic Effects



Why use them?

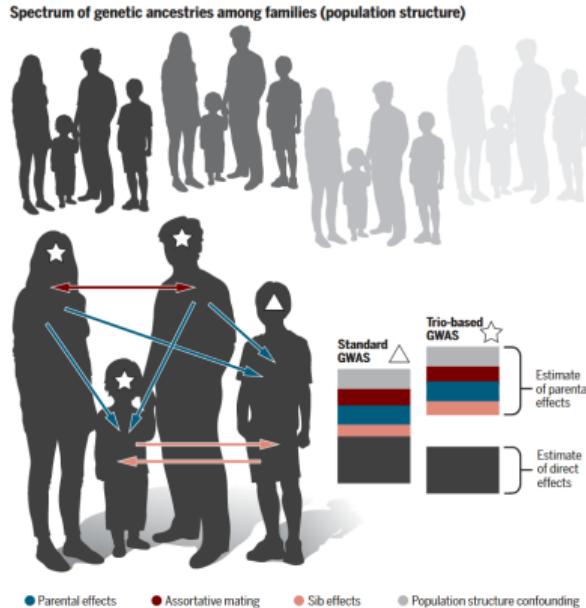


Figure 8: Signals captured by FGWAS in families
(Young et al. 2019, *Science*).

Unbiased GWAS

- ▶ Can discriminate **DGEs^a** and **Population Effects** using **parental genotypes** as controls.
- ▶ Source of genetic variation is *within-family*.

We lose power

- ▶ We need **more individuals n** to be genotyped.

^aDirect Genetic Effects



Why use them?

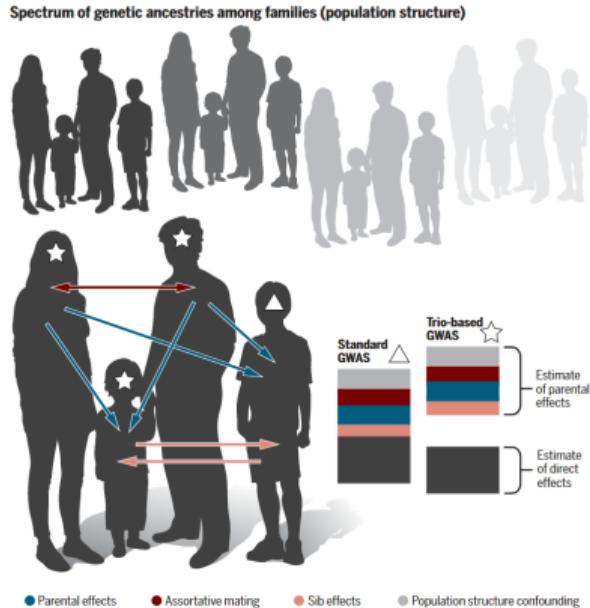


Figure 8: Signals captured by FGWAS in families
(Young et al. 2019, *Science*).

Unbiased GWAS

- ▶ Can discriminate **DGEs^a** and **Population Effects** using **parental genotypes** as controls.
- ▶ Source of genetic variation is *within-family*.

We lose power

- ▶ We need **more individuals n** to be genotyped.
- ▶ Complete parent-offspring trios are *rare* in cohorts.

^aDirect Genetic Effects



References



García-Ortiz, H., Barajas-Olmos, F., Contreras-Cubas, C.,
Cid-Soto, M. Á., Córdova, E. J.,
Centeno-Cruz, F., Mendoza-Caamal, E.,
Cicerón-Arellano, I., Flores-Huacuja, M.,
Baca, P., Bolnick, D. A., Snow, M.,
Flores-Martínez, S. E., Ortiz-Lopez, R.,
Reynolds, A. W., Blanchet, A.,
Morales-Marín, M., Velázquez-Cruz, R.,
Kostic, A. D., ... Orozco, L. (2021). *Nature Communications*, 12(1), 5942.
<https://doi.org/10.1038/s41467-021-26188-w>



Tapia-Conyer, R., Kuri-Morales, P., Alegre-Díaz, J.,
Whitlock, G., Emberson, J., Clark, S., Peto, R.,
& Collins, R. (2006). *International Journal of*

Epidemiology, 35(2), 243–249.
<https://doi.org/10.1093/ije/dyl042>



Young, A. I., Benonisdottir, S., Przeworski, M., & Kong, A. (2019). *Science*, 365(6460), 1396–1400.
<https://doi.org/10.1126/science.aax3710>



Ziyatdinov, A., Torres, J., Alegre-Díaz, J., Backman, J.,
Mbatchou, J., Turner, M., Gaynor, S. M.,
Joseph, T., Zou, Y., Liu, D., Wade, R.,
Staples, J., Panea, R., Popov, A., Bai, X.,
Balasubramanian, S., Habegger, L., Lanche, R.,
Lopez, A., ... Tapia-Conyer, R. (2023). *Nature*, 622(7984), 784–793.
<https://doi.org/10.1038/s41586-023-06595-3>