Prior preeclampsia or chronic hypertension present distinct molecular subtypes in hypertensive disorders of pregnancy

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OBJECTIVE

- **Hypertensive disorders of pregnancy (HDP) are major causes of maternal and fetal morbidity and mortality.**
- **Previously, elevated PAPPA2 expression in cfRNA was identified as predictive of preeclampsia (PE) in a dose-dependent manner, with an exceptionally strong effect size among individuals without preexisting high risk conditions.**
- **Here we evaluate PAPPA2 expression based on HDP and gestational age (GA) at delivery in those with chronic hypertension (CHTN) or prior PE.**

STUDY DESIGN

- Whole blood and medical information were collected from a diverse group of 5,399 study participants collected across 11 clinical sites and direct-to-participant recruitment (Table 1).
- Spontaneous preterm births were excluded.
- cfRNA was extracted and analyzed by sequencing to generate gene counts.
- Robust linear regression evaluated PAPPA2 dependence on delivery GA by preterm PE status.

REFERENCES
Elovitz MA, Gee EPS, Delaney-Busch N, et al. Molecular subtyping of hypertensive disorders of pregnancy. Nat Commun. 2025;16(1):2948. doi:10.1038/s41467-025-58157-y

One biomarker does not fit all –

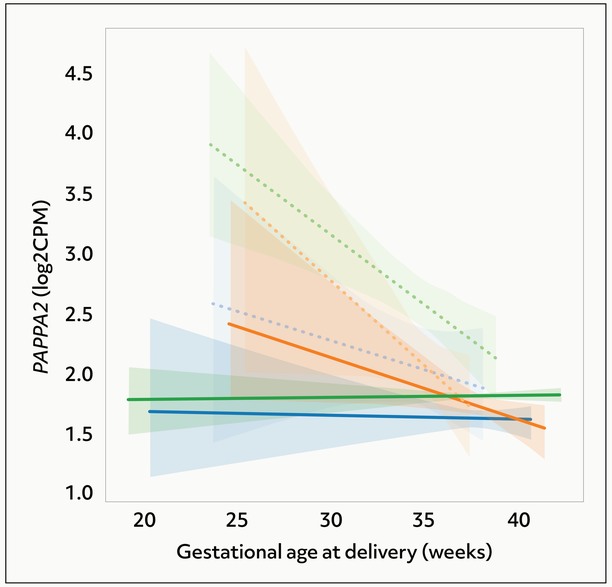
Recurrent preeclampsia has molecular patterns similar to de novo preeclampsia, in contrast with superimposed preeclampsia.

Table 1 - Summary of participant characteristics.
PE = Preeclampsia
CHTN = Chronic Hypertension
BMI = Body-Mass Index
GA= Gestational Age

*Preterm PE includes those diagnosed with PE <37 weeks leading to preterm birth (<37 wks) and/or severe features.

	Prior PE (n=278)		CHTN (n=308)	
	Preterm PE* (n=29)	Not preterm PE (n=249)	Preterm PE* (n=27)	Not preterm PE (n=281)
Prior PE, n	29	249	0	0
CHTN, n	0	0	27	281
Type I/II diabetes, n	0	0	0	0
Age, mean (min-max)	32.3 (23-44)	31.0 (19.2-44.2)	32.3 (24.9-42.1)	31.6 (19.6-45.2)
BMI, mean (min-max)	32.8 (20.1-51.4)	30.7 (19.0-61.6)	38.5 (25.5-64.5)	36.1 (17.2-74.5)
Nullparous, n	0	0	14	114
Delivery GA, mean (min-max)	34.9 (25.4-37.4)	38.3 (24.6-41.4)	34.6 (23.7-38.1)	37.8 (20.3-40.7)
All PE, n	29	38	27	40
Asian, n	0	10	0	2
Black, n	9	64	11	103
Hispanic, n	4	41	4	22
Multiracial, n	1	18	1	21
White, n	15	116	11	133

Figure 2 - PAPPA2 counts (log2 count per million) measured mid-trimester as a function of gestational age at delivery. Colored by preexisting high risk condition, blue CHTN only, orange Prior PE, green no preexisting risk condition. Lighter shades represent cases of preterm PE including those diagnosed with PE <37 weeks leading to preterm birth (<37 wks) and/or severe features. r^2, Pearson correlation; p, p-value using two-sided Wald test to test the null hypothesis that the slope is zero; PE = Preeclampsia; CHTN = Chronic Hypertension



RESULTS

- **In individuals with chronic hypertension there was no significant correlation between PAPPA2 expression level and gestational age at delivery regardless of the occurrence of either preterm PE (n=27, r^2=2.8%, p=0.4, Fig1) or a pregnancy where preterm PE did not occur (n=281, r^2=0%, p=0.85, Fig1).**
- However in individuals with a history of PE, a significant correlation with PAPPA2 was observed in those who developed preterm PE (n=29, r^2=16.6%, p=0.028, Fig1), but in those who did not develop preterm PE the relationship was not significant (n=249, r^2=1.1%, p=0.09, Fig1).
- This is similar to the previously reported effect among individuals without preexisting high risk conditions who develop preterm PE (n=87, r^2=12.2%, p<0.001, Fig1).

CONCLUSION

- **The molecular pattern is different in superimposed PE where no elevation in PAPPA2 was observed.**
- Molecular patterns observed for PAPPA2 in individuals without preexisting risk are replicated in individuals with prior PE who go on to have repeated PE.
- These findings support multiple etiologies of HDP and the potential for personalized treatments paths in the future.
- Due to underlying biological differences, predictive screening tools must demonstrate validity in those with chronic hypertension, those with prior preeclampsia, and those without pre-existing high risk conditions to be clinically useful.

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