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Data Article

Effect of parental origin of damaging variants in pro-angiogenic genes on fetal growth in patients with congenital heart defects: Data and analyses

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ABSTRACT

The placenta is a highly vascular structure composed of both maternal and fetal elements. We have determined that damaging

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variants in genes responsible for the positive regulation of angiogenesis (PRA) (GO:0045766) that are inherited by the fetus impair fetal growth and placental function in pregnancies involving critical congenital cardiac defects (Russell et al., 2019). In this dataset, we present the specific genetic variants identified, describe the parental origin of each variant where possible and present the analyses regarding the potential effects of parental origin of the variant on placental function and fetal growth. The data presented are related to the research article "Damaging variants in pro-angiogenic genes impair growth in fetuses with cardiac defects" (Russell et al., 2019).

Specifications Table

Subject area	*Biology*
More specific subject area	*Molecular Genetics*
Type of data	*Tables*
How data was acquired	*Whole exome sequencing was performed as described in the related research article [1]. Exons were captured from fragmented and adaptor ligated genomic DNA samples using the SureSelect Human All Exon v.5 containing* 51 Mb *(Agilent Technologies, Santa Clara, CA). Paired-end 2x101-base massively parallel sequencing was carried out on the Illumina HiSeq2500 platform (Illumina, San Diego, CA), according to the manufacture's protocols. Base calling was performed by the Illumina CASAVA software (version 1.8.2) with default parameters.*
Data format	*Analyzed*
Experimental factors	*Sequencing reads were aligned to the human reference genome (GRCh37-derived alignment set used in 1000 Genomes Project) and the Genome Analysis Toolkit (GATK, v.2.6–5) was used to generate variant calls as previously described [1].*
Experimental features	*Families delivering a baby with a congenital heart defect (CHD) requiring surgical repair in infancy were recruited for the study. Experimental methods were described in the related research article.[1] Briefly,* *(i) The placenta and neonate were weighed and measured.* *(ii) Exome sequencing was performed on the subjects (N = 133) and their parents (N = 114 parent-child trios and 15 parent-child duos).* *(iii) The GeneVetter analysis tool (default settings) was used to identify damaging coding sequence variants in genes identified as positive regulators of angiogenesis (PRA) (GO:0045766).* *(iv) The effect of inherited and not inherited parental damaging PRA variants on placental function and fetal growth were examined.*
Data source location	*Data source: Division of Cardiothoracic Surgery, The Children's Hospital of Philadelphia, Philadelphia, PA* *Data analysis: Division of Pediatric Cardiology, Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI*
Data accessibility	*All of the data is presented in this article. The subjects were not consented for the raw sequence data to be released to a public database so what is presented is the analyzed and summarized data.*
Related research article	*M.W. Russell, J.S. Moldenhauer, J. Rychik, N.B. Burnham, E. Zullo, S.I. Parry, R.A. Simmons, M.A. Elovitz, S.C. Nicolson, R.L. Linn, M.P. Johnson, S. Yu, M.G. Sampson, H. Hakonarson, J.W. Gaynor. Damaging variants in pro-angiogenic genes impair growth in fetuses with cardiac defects. J Pediatr. 2019 Jun 18;.* https://doi.org/10.1016/j.jpeds.2019.05.013. *[Epub ahead of print] PubMed PMID: 31227283.*

Value of the data

- The presented data will facilitate the evaluation of fetal and maternal genetic variation on placental function and fetal growth in pregnancies involving a fetus with a CHD.
- The data will directly benefit investigators examining the relationship between fetal growth and development and clinical outcomes in infants with critical CHD.
- In the accompanying tables, different ways of grouping the data are used to examine the effects of inherited and not inherited genetic variation on placental function and fetal growth. The value of the data will be in the stimulation of ideas and approaches to estimate these complex genetic relationships.
- Of particular interest is the potential interaction effect of damaging PRA variants present in both the mother and fetus. The interaction effect will require a much larger cohort to adequately assess; the presentation of the aggregate data using several different approaches will allow merging of the data with that from ongoing and future efforts.

1. Data

We performed exome sequencing on infants with critical congenital heart disease (N = 133) and their parents (N = 114 parent-child trios and 15 parent-child duos). Using the GeneVetter program, we

Table 1
Positive Regulation of Angiogenesis (PRA) gene set (GO:0045766).

Positive Regulation of Angiogenesis (PRA)			
ABL1	CX3CR1	HSPB1	PTGS2
ACVRL1	CXCL8	HSPB6	PTK2B
ADAM12	CXCR2	HYAL1	RAMP2
ADM	CYBB	IL10	RAPGEF3
ADM2	CYP1B1	IL1A	RHOB
AGGF1	CYSLTR2	IL1B	RHOJ
AGO2	DDAH1	ISL1	RLN2
AGTR1	DLL1	ITGA5	RRAS
AKT3	ECM1	ITGB1	RUNX1
ANGPT2	Emilin2	ITGB2	S100A1
ANGPT4	ENG	ITGB8	SASH1
ANGPTL3	EPHA1	JAK1	SEMA5A
ANGPTL4	ERAP1	JCAD	SERPINE1
ANXA1	ETS1	JUP	SFRP2
ANXA3	F3	KDR	SIRT1
APELA	FGF1	KLF4	SIRT6
APLNR	FGF18	LRG1	SMAD1
AQP1	FGF2	MAP3K3	SMOC2
BMPER	FGFBP1	MTDH	SP1
BRCA1	FLT1	MYDGF	SPHK1
BTG1	FOXC2	NFE2L2	SRPX2
C3	GAB1	NODAL	STAT3
C3AR1	GATA2	NOS3	STIM1
C5	GATA4	NR2E1	TBXA2R
C5AR1	GATA6	NRP1	TEK
C6	GDF2	PAK4	TN-W
CCBE1	GHRL	PDCD6	TERT
CCL11	GHSR	PDCL3	TGFBR2
CCL24	GREM1	PDPK1	THBS1
CCR3	HDAC7	PGF	TLR3
CD34	HDAC9	PIK3C2A	TMIGD2
CD40	HGF	PIK3R6	TNFSF12
CDH5	HIF1A	PLCG1	TWIST1
CELA1	HIPK1	PLK2	UTS2R
CHI3L1	HIPK2	PPP1R16B	VASH2
CHRNA7	HK2	PRKCA	VEGFA
CIB1	HMGA2	PRKCB	VEGFB
CMA1	HMGB1	PRKD1	VEGFC
CTSH	HMOX1	PRKD2	VEGFD
CX3CL1	HPSE	PTGIS	WNT5A
			XBP1
			ZC3H12A
			ZNF304

Table 2
Sequence variants identified as damaging by GeneVetter analysis in the 163 positive regulator of angiogenesis (PRA) genes (GO:0045766) in the cohort.

Subject id	gene	chr:pos:ref:alt	id	aa change
C57	ABL1	9:133738189:G:A	rs150134901	E216K
C1	ADAM12	10:127738138:G:C	.	C573W
C17	ADAM12	10:127737958:T:C	rs77297117	N597S
C135	ADAM12	10:127737958:T:C	rs77297117	N597S
C44	ANGPT2	8:6371240:C:G	rs149383060	L386F
C84	ANGPT2	8:6371240:C:G	rs149383060	L386F
C59	ANXA3	4:79522685:C:T	rs5949	P251L
C87	AQP1	7:30961780:C:T	.	R222C
C120	AQP1	7:30961753:G:A	rs200906195	V213M
C73	BRCA1	17:41246709:G:C	rs80357199	A280G
C121	BRCA1	17:41243948:C:G	.	Q1200H
C44	BRCA1	17:41256200:C:A	.	S127I
C95	C3	19:6693489:T:A	.	Q1055L
C47	C3	19:6686180:C:G	rs371629277	W1255C
C132	C6	5:41203257:G:T	.	H26N
C66	C6	5:41150035:A:G	rs76202909	
C134	C6	5:41150035:A:G	rs76202909	
C95	CCBE1	18:57364474:G:T	rs191999971	T34N
C26	CCR3	3:46307313:A:G	rs138346219	I243V
C131	CCR3	3:46307313:A:G	rs138346219	I243V
C132	CCR3	3:46306845:C:T	rs201795127	R87X
C46	CCR3	3:46307064:G:A	rs145141172	V160M
C5	CD34	1:208084424:A:G	rs370283469	M1T
C89	CD34	1:208072436:G:A	rs148688256	T133I
C135	CD34	1:208072436:G:A	rs148688256	T133I
C56	CDH5	16:66420973:G:A	.	A158T
C51	CDH5	16:66436582:G:A	rs139612718	R622Q
C44	CHI3L1	1:203152888:G:A	rs199779694	R116C
C39	CHI3L1	1:203154465:C:T	rs146010120	R35Q
C128	CHI3L1	1:203154468:T:C	.	Y34C
C112	CHRNA7	15:32393507:A:T	.	D95V
C15	CHRNA7	15:32450712:A:G	rs142728508	Y262C
C125	CIB1	15:90774612:G:A	.	S108F
C129	CTSH	15:79224791:C:T	.	G139S
C28	CYP1B1	2:38298338:C:T	.	E387K
C48	CYP1B1	2:38298028:T:A	.	Q490L
C108	CYP1B1	2:38298028:T:A	.	Q490L
C1	CYP1B1	2:38302045:G:A	rs104894978	R163C
C90	CYP1B1	2:38301574:C:A	rs72549382	V320L
C70	CYP1B1	2:38297867:A:T	rs368552668	X544K
C70	EMILIN2	18:2913203:A:T	.	E988V
C89	EMILIN2	18:2913098:T:A	.	L953Q
C65	EPHA1	7:143092241:C:A	.	E706D
C30	EPHA1	7:143095083:T:G	.	R515S
C13	EPHA1	7:143095862:C:T	.	V390M
C18	ETS1	11:128354768:T:C	.	K271R
C40	FGF1	5:141993631:C:T	rs17223632	G21E
C67	FGF1	5:141993631:C:T	rs17223632	G21E
C66	FGF18	5:170883784:G:A	rs371575721	R200Q
C68	FLT1	13:28919631:G:A	rs200840674	A769V
C13	FLT1	13:28885760:G:A	rs140861115	P1201L
C81	FLT1	13:28885760:G:A	rs140861115	P1201L
C75	FOXC2	16:86602433:T:C	rs61753346	C498R
C56	FOXC2	16:86602272:A:G	rs147258453	Q444R
C37	GAB1	4:144359333:T:C	rs201252337	Y259H
C75	GDF2	10:48414216:C:T	rs142402214	D218N

Table 2 (*continued*)

Subject id	gene	chr:pos:ref:alt	id	aa change
C114	GDF2	10:48414216:C:T	rs142402214	D218N
C32	GHRL	3:10328465:A:G	rs376322935	L86P
C120	HDAC7	12:48183606:C:T	rs200899015	R711H
C123	HDAC9	7:18629974:C:G	.	L94V
C89	HGF	7:81374380:A:C	rs139457161	S228A
C133	HIF1A	14:62194346:A:C	rs373399672	D273A
C21	HIPK2	7:139285223:C:T	rs56132157	R792Q
C89	HK2	2:75105946:C:T	.	A388V
C129	HK2	2:75113788:C:T	rs146476722	P736L
C115	HK2	2:75106029:G:A	.	V416I
C134	HPSE	4:84243462:C:T	.	G95S
C5	HPSE	4:84216649:G:A	rs144185023	Q494X
C140	HPSE	4:84216649:G:A	rs144185023	Q494X
C26	HSPB1	7:75932109:G:C	rs367662394	R27P
C103	HYAL1	3:50338090:C:T	.	A378T
C124	HYAL1	3:50339969:T:C	.	N140S
C37	IL1A	2:113541307:C:G	rs150033245	C14S
C9	ITGB2	21:46308800:C:T	rs2230531	E630K
C139	ITGB2	21:46308800:C:T	rs2230531	E630K
C140	ITGB2	21:46308800:C:T	rs2230531	E630K
C73	JUP	17:39925401:C:T	rs144171604	R176Q
C12	KLF4	9:110249816:G:A	rs139237114	H287Y
C137	MAP3K3	17:61767648:G:A	.	R394H
C120	NFE2L2	2:178096406:G:A	rs141363120	L309F
C44	NOS3	7:150693897:G:A	rs141456642	E156K
C137	NOS3	7:150693897:G:A	rs141456642	E156K
C132	NOS3	7:150706545:C:T	rs368180942	P795L
C16	NOS3	7:150709452:C:T	.	R1000W
C55	NOS3	7:150707257:G:A	rs201579252	R856H
C18	NRP1	10:33515198:C:T	.	R334H
C62	PAK4	19:39668385:C:G	.	P519R
C52	PAK4	19:39666005:C:T	rs377696830	S429L
C89	PDPK1	16:2627442:C:G	.	F242L
C109	PIK3C2A	11:17150917:C:T	rs149664988	D777N
C115	PIK3C2A	11:17172056:A:G	rs138300747	F439S
C32	PIK3C2A	11:17191207:T:C	rs142132566	K28E
C94	PIK3C2A	11:17140241:G:A	.	L996F
C60	PIK3C2A	11:17126742:T:C	.	N1219D
C68	PIK3C2A	11:17150848:G:A	rs201036447	R800W
C5	PLCG1	20:39801462:A:T	rs147844565	D1075V
C27	PLK2	5:57755583:C:A	rs372211010	E68D
C4	PRKD1	14:30396699:A:G	.	L7P
C96	PTGIS	20:48164484:G:A	rs200631702	R91C
C40	PTGS2	1:186648228:G:A	.	P92L
C93	RAPGEF3	12:48137442:G:A	rs200527655	R566W
C112	RAPGEF3	12:48131987:C:T	rs200517997	S857N
C138	RAPGEF3	12:48141598:T:C	rs146484121	Y457C
C44	RHOJ	14:63749908:G:A	rs150345688	E158K
C100	RHOJ	14:63747854:G:T	rs372472368	
C73	SASH1	6:148865872:G:A	rs75149315	R1089Q
C111	SASH1	6:148865872:G:A	rs75149315	R1089Q
C133	SASH1	6:148867217:C:T	rs200999161	R1139W
C104	SASH1	6:148869462:G:A	rs143577116	R1171Q
C115	SERPINE1	7:100780350:C:T	.	R386W
C43	SP1	12:53776845:C:G	.	Q372E
C100	TEK	9:27169568:C:T	.	S190L
C108	UTS2R	17:80332489:G:A	rs201963255	D97N

Chr:pos:ref:alt: (Chromosome:position:reference nucleotide; “altered” or substituted nucleotide) refers to the location of the genetic alteration with the position referring to the GRCh37/hg19 Assembly.

Table 3
Effect of parental damaging PRA variants on placental function and fetal growth. The data is evaluated from the fetal perspective. For example, for the question, "Was there a variant in the father that was inherited by the infant?", the "No" answer will include cases in which the father had no variants and cases in which the father did have a variant but it wasn't inherited by the proband.

		Available N	Weight z-score	Height z-score	Head circumference z-score	UA PI z-score
Was there a variant in the father that was inherited by the infant?	Yes	41	−0.11 ± 0.92	−0.12 ± 1.3	−0.51 ± 1.1	1.28 ± 1.3
	No	72	0.01 ± 0.88	−0.04 ± 1.4	−0.13 ± 1.2	0.79 ± 1.4
		P-value	*0.53*	*0.77*	*0.10*	*0.11*
Was there a variant in the father that wasn't inherited by the infant?	Yes	46	0.05 ± 0.87	−0.07 ± 1.2	−0.12 ± 1.1	0.82 ± 1.3
	No	64	−0.10 ± 0.92	−0.06 ± 1.4	−0.40 ± 1.3	0.99 ± 1.4
		P-value	*0.40*	*0.97*	*0.22*	*0.59*
Was there a variant in the mother that was inherited by the infant?	Yes	40	−0.34 ± 0.89	−0.60 ± 1.3	−0.67 ± 1.1	1.08 ± 1.3
	No	88	0.01 ± 0.95	0.05 ± 1.5	−0.12 ± 1.2	0.80 ± 1.4
		P-value	*0.053*	*0.02*	*0.01*	*0.34*
Was there a variant in the mother that wasn't inherited by the infant?	Yes	47	0.04 ± 0.89	0.04 ± 1.5	−0.26 ± 1.1	0.86 ± 1.4
	No	81	−0.18 ± 0.97	−0.27 ± 1.4	−0.31 ± 1.2	0.92 ± 1.3
		P-value	*0.19*	*0.26*	*0.79*	*0.83*

* Data are presented as Mean ± Standard deviation.
§ P-value from two-sample t-test.

identified 113 pathogenic variants in the 163 positive regulators of angiogenesis (PRA) genes (Table 1) in 73 subjects (see Table 2 for specific variants identified in the probands). To estimate the effects of the parental damaging PRA variants on placental function and fetal growth, we grouped the data to examine the effects from different perspectives. First, we examined the effects from the fetal perspective to assess whether a variant inherited or not inherited from either parent had an effect on placental function and fetal growth (Table 3). To remove the effects of having variants in both parents, we next restricted analysis to those cases where only a single parent had identified pathogenic variants (Table 4). Lastly, to specifically assess the effects of maternal variants on placental function and fetal growth, we grouped all cases based on the presence or absence of maternal variants that were inherited or not inherited (Table 5). The presented data will allow the examination of the effects of parental origin of inherited and not inherited variants on placental function and fetal growth in pregnancies involving CHD. In addition, it is anticipated that the different approaches to grouping the

Table 4
Effect of parental origin of damaging PRA variants on placental function and fetal growth. The data only includes those cases in which inherited variants or not inherited variants originate from a single parent. For example, for the question, "Was there a variant in the father that was inherited by the infant?", the "Yes" answer includes only those cases in which one or more variants were inherited from the father and no variants were inherited from the mother. Similarly, for the question, "Was there a variant in the father that wasn't inherited by the infant?", only those cases in which no PRA variant was noted in the proband and there were 1 or more variants in the father were included.

		Available N	Weight z-score	Height z-score	Head circumference z-score	UA PI z-score
Was there a variant in the father that was inherited by the infant?	Yes	25	0.01 ± 0.97	−0.02 ± 1.4	−0.26 ± 1.0	1.36 ± 0.71
Was there a variant in the mother that was inherited by the infant?	Yes	24	−0.37 ± 0.95	−0.82 ± 1.4	−0.51 ± 1.1	1.03 ± 0.44
		P-value	*0.17*	*0.054*	*0.41*	*0.43*
Was there a variant in the father that wasn't inherited by the infant?	Yes	31	−0.04 ± 0.85	−0.22 ± 1.1	−0.18 ± 1.1	0.58 ± 0.05
Was there a variant in the mother that wasn't inherited by the infant?	Yes	32	−0.04 ± 0.88	−0.06 ± 1.7	−0.39 ± 1.2	0.70 ± 0.18
		P-value	*0.97*	*0.65*	*0.48*	*0.74*

*Data are presented as Mean ± Standard deviation.
§ P-value from two-sample t-test.

Table 5
Effect of maternal damaging PRA variants on placental function and fetal growth. The data specifically examines the effects of maternal PRA variants. All probands with maternal data are included in the analysis. Each subject was assigned to one of the six categories based on variant distribution.

		Available N	Weight z-score	Height z-score	Head circumference z-score	UA PI z-score
No damaging variant in infant	No damaging variant in mother	37	0.09 ± 0.99	0.21 ± 1.2	0.14 ± 1.3	0.65 ± 1.4
	1 or more damaging variant in mother	20	0.12 ± 0.65	0.27 ± 1.7	−0.33 ± 1.0	0.44 ± 1.5
		P-value	*0.90*	*0.91*	*0.17*	*0.64*
1 damaging variant in infant	Not inherited from mother	25	−0.26 ± 1.1	−0.43 ± 1.8	−0.29 ± 1.1	1.14 ± 0.97
	Inherited from mother	18	−0.14 ± 1.0	−0.72 ± 1.5	−0.49 ± 1.3	1.45 ± 1.0
		P-value	*0.70*	*0.58*	*0.57*	*0.40*
2 + damaging variants in infant	None inherited from mother	6	−0.05 ± 1.0	−0.03 ± 1.2	−0.46 ± 0.90	1.96 ± 2.0
	At least one inherited from mother	22	−0.42 ± 0.79	−0.43 ± 1.1	−0.79 ± 1.1	0.81 ± 1.4
		P-value	*0.35*	*0.44*	*0.50*	*0.14*

* Data are presented as Mean ± Standard deviation.
§ P-value from two-sample t-test.

cases for analysis will help in the design and analysis of future work examining parental genetic factors impacting the maternal-fetal environment and fetal growth.

2. Experimental design, materials, and methods

For a complete description of the experimental design and methods, please see the related research article [1]. Briefly, whole exome sequencing was performed on 133 subjects and all consented parents (114 parent-child trios, 15 parent-child duos and 4 child only). Exons were captured from fragmented and adaptor ligated genomic DNA samples using the SureSelect Human All Exon v.5 containing 51 Mb (Agilent Technologies, Santa Clara, CA). Paired-end 2 × 101-base massively parallel sequencing was carried out on the Illumina HiSeq2500 platform (Illumina, San Diego, CA), according to the manufacture's protocols. Base calling was performed by the Illumina CASAVA software (version 1.8.2) with default parameters. Sequencing reads passing the quality filter were aligned to the human reference genome (GRCh37-derived alignment set used in 1000 Genomes Project) with Burrows-Wheeler Aligner (BWA, v.0.7.12) and Dragen (Illumina, San Diego, CA) [2]. PCR duplicates were removed using Picard (v.1.97; Broad Institute, Boston, MA). The Genome Analysis Toolkit (GATK, v.2.6−5; Broad Institute, Boston, MA) was used to generate variant calls. The Gene Ontology (GO) database was used to identify the target gene set. The GO term "positive regulator of angiogenesis" (PRA) (GO:0045766) was selected to minimize potential opposing effects of damaging variants in positive and negative regulators. The PRA gene set contains 163 genes (Table 1). Damaging variants in the PRA gene set were identified using the GeneVetter program, a web-based analysis tool designed to improve the accuracy of pathogenicity prediction for single nucleotide variants identified by exome sequencing [3]. To be adjudicated as damaging by using the program's default settings, a variant must meet all of the following criteria: (i) have a maximum allele frequency in the sample population of <0.05, (ii) be adjudicated as "Damaging" by at least 2 of 3 of the following algorithms: PolyPhen2, SIFT, and MutationTaster, and (iii) have a maximum allele frequency across European-Americans and African-Americans of <0.005.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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