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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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).

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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 manufacturer’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. 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.J. 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.
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

| Positive Regulation of Angiogenesis (PRA) gene set (GO:0045766). |
|---------------------------------------------------------------|
| ABL1 | CX3CR1 | HSPB1 | PTGS2 |
| ACVR1L1 | CXCL8 | HSPB6 | PTK2B |
| ADAM12 | CXCR2 | HYAL1 | RAMP2 |
| ADM | CYBB | IL10 | RAFGEF3 |
| ADM2 | CYP1B1 | IL1A | RHOB |
| AGGF1 | CYSTK2 | IL1B | RH0J |
| AGO2 | DDAH1 | ISL1 | RLT2 |
| AGTR1 | DLL1 | ITGA5 | RRAS |
| AKT3 | ECM1 | ITGB1 | RUNX1 |
| ANGPT2 | Emelin2 | 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 | S1 |
| BRCAl | FLT1 | MYDGF | SIKH1 |
| BTG1 | FOXC2 | NFE2L2 | SPPX2 |
| C3 | GAB1 | NODAL | STAT3 |
| C3AR1 | GATA2 | NOS3 | STIM1 |
| C5 | GATA4 | NR2E1 | TBX2AR |
| CSAR1 | GATA6 | NRP1 | TEK |
| C6 | GDF2 | PAK4 | TN-W |
| CCB1 | GHR1 | PDCD6 | TERT |
| CCL11 | GHSR | PDCD3 | THBS1 |
| CCL24 | GREM1 | PDLP1 | TGFBR2 |
| CCR3 | HDAC7 | PGF | TLR3 |
| CD34 | HDAC9 | PIK3C2A | TIMGD2 |
| CD40 | HGF | PIK3R6 | TNFSF12 |
| CDH5 | HIF1A | PLCG1 | TWIST1 |
| CELA1 | HIPK1 | PKL2 | UTS2R |
| CH33L1 | HIPK2 | PPI1R16B | VASH2 |
| CHRNA7 | HK2 | PRKCA | VEGFA |
| CIB1 | HMGA2 | PRKCB | VEGFB |
| CMA1 | HMGB1 | PRKD1 | VEGFC |
| CTS1 | HMOX1 | PRKD2 | VEGFD |
| CX3CL1 | HPSE | PTGS | 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 | rs20096195 | V213M     |
| C73        | BRCA1 | 17:41246709:C:G | rs80357199 | A280G     |
| C121       | BRCA1 | 17:41243948:C:T |       | Q1200H    |
| C44        | BRCA1 | 17:41256200:C:A |       | S127I     |
| C95        | C3   | 19:6693489:T:A  |       | Q1055L    |
| C47        | C3   | 19:6686180:G:C  | rs371629277 | W1255C   |
| C132       | C6   | 5:41203257:C:T |       |           |
| C66        | C6   | 5:41150035:A:G  |       | H26N      |
| C134       | C6   | 5:41150035:A:G  |       |           |
| C95        | CCEB1 | 18:57364474:G:T | rs191999971 | T34N      |
| C26        | CCR3 | 3:46307033:A:G  | rs138346219 | I243V    |
| C131       | CRC3 | 3:46307033:A:G  | rs138346219 | I243V    |
| C132       | CCR3 | 3:46306845:C:T  | rs201795127 | R87X     |
| C46        | CCR3 | 3:46306064:A:G  | rs145141172 | V160M    |
| C5         | CD34 | 1:208084424:G:A | rs370283469 | M1T      |
| C89        | CD34 | 1:208072436:G:A | rs148688256 | T133I    |
| C135       | CD34 | 1:208072436:G:A | rs148688256 | T133I    |
| C56        | CDH5 | 16:66420973:G:A |       |           |
| C51        | CDH5 | 16:66423682:G:A | rs139612718 | R622Q    |
| C44        | CHI3L1 | 1:203152888:G:A | rs199779694 | R116C    |
| C39        | CHI3L1 | 1:20315465:C:T | rs146010120 | R35Q     |
| C128       | CHI3L1 | 1:20315468:C:T |       | Y34C     |
| C112       | CHRNA7 | 15:32939507:C: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        | EMLIN2 | 18:2913203:A:T  |       | E988V    |
| C89        | EMLIN2 | 18:2913098:T:A  |       | L953Q    |
| C65        | EPH1A | 7:143092241:C:A  |       | E706D    |
| C30        | EPH1A | 7:143095083:T:G  |       | R515S    |
| C13        | EPH1A | 7:143095862:C:T  |       | V390M    |
| C18        | ETS1 | 11:128345768:C:T |       | K271R    |
| C40        | FGFR1 | 5:141993631:C:T  | rs17223632 | G21E     |
| C67        | FGFR1 | 5:141993631:C:T  | rs17223632 | G21E     |
| C66        | FGFR1 | 5:170837384:G:A  | rs371575721 | R200Q    |
| C68        | FLT1 | 13:28919631:G:A  | rs200840674 | A769V    |
| C13        | FLT1 | 13:28865760:G:A  | rs140861115 | P1201L   |
| C81        | FLT1 | 13:28865760:G:A  | rs140861115 | P1201L   |
| C75        | FOXC2 | 16:86602433:C:T  | 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    |
| Subject id | gene   | chr:pos:ref:alt | id        | aa change |
|------------|--------|----------------|-----------|-----------|
| C114       | GDF2   | 10:4814216:C:T | rs142402214 | D218N     |
| C122       | GHRF1  | 3:10225865:A:G | rs376225935 | L86P      |
| C120       | HDAC7  | 12:48183606:C:T | rs200899015 | R71H      |
| C123       | HDAC9  | 7:18629974:C:G | .          | L94V      |
| C89        | HGF    | 7:81374380:A:C | rs139571616 | S228A     |
| C133       | HIF1A  | 14:62194346:A:C | rs373399672 | D273A     |
| C21        | HIPK2  | 7:139285223:C:T | rs56132157  | R79Q      |
| C89        | HK2    | 2:75105946:C:T | .          | A388V     |
| C129       | HK2    | 2:75113788:C:T | rs146476722 | P736L     |
| C115       | HK2    | 2:75106029:C:A | .          | V416I     |
| C134       | HPSE   | 4:84243462:C:T | .          | G95S      |
| C5         | HPSE   | 4:84216649:A:G | rs14185023  | Q494X     |
| C140       | HPSE   | 4:84216649:A:G | rs14185023  | Q494X     |
| C26        | HSPB1  | 7:75932109:C:G | rs36762394  | R27P      |
| C103       | HYAL1  | 3:50338090:C:T | .          | A378T     |
| C124       | HYAL1  | 3:50339969:T:C | .          | N140S     |
| C37        | IL1A   | 2:113541307:C:G | rs150323245 | C145      |
| C9         | ITGB2  | 21:46308000:C:T | rs22235031  | E630K     |
| C139       | ITGB2  | 21:46308000:C:T | rs22235031  | E630K     |
| C140       | ITGB2  | 21:46308000:C:T | rs22235031  | E630K     |
| C73        | JUP    | 17:39925401:C:T | rs144171604 | R176Q     |
| C12        | KLF4   | 9:110249816:C:G | rs139237114 | H827Y     |
| C137       | MAP3K3 | 17:61767648:C:A | .          | R394H     |
| C120       | NFE2L2 | 2:178096406:C:G | rs141363120 | L309F     |
| C44        | NO3    | 7:150093897:C:G | rs14156642  | E156K     |
| C137       | NO3    | 7:150093897:C:G | rs14156642  | E156K     |
| C132       | NO3    | 7:150706545:C:T | rs368180942 | P975L     |
| C16        | NO3    | 7:150706942:C:T | .          | R1000W    |
| C55        | NO3    | 7:150707257:C:G | 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       | PIK3CA | 11:17150917:C:T | rs149664988 | D777N     |
| C115       | PIK3CA | 11:17172056:A:G | rs138300747 | F439S     |
| C32        | PIK3CA | 11:17191207:C:T | rs142132566 | K28E      |
| C94        | PIK3CA | 11:17140241:C:G | .          | L996F     |
| C60        | PIK3CA | 11:17126742:C:T | .          | N1219D    |
| C68        | PIK3CA | 11:17150848:C:G | rs20106447  | R800W     |
| C5         | PLCG1  | 20:39804162:A:T | rs147844565 | D1075V    |
| C27        | PLK2   | 5:7755583:C:G   | rs372211010 | E68D      |
| C4         | PRKD1  | 14:30396699:A:G | .          | L7P       |
| C96        | PTGIS  | 20:48164484:C:G | rs200631702 | R91C      |
| C40        | PTGS2  | 18:36648228:C:G | .          | P92L      |
| C93        | RAPGEF3| 12:48137442:C:G | rs200527655 | R566W     |
| C112       | RAPGEF3| 12:48131987:C:T | rs20051799  | S857N     |
| C138       | RAPGEF3| 12:48141598:C:T | rs14648121  | Y457C     |
| C44        | RHOC   | 14:63749908:C:G | rs150345688 | E158K     |
| C100       | RHOC   | 14:63747854:C:G | rs372472638 | .         |
| C73        | SASH1  | 6:148865872:C:G | rs75149315  | R1089Q    |
| C111       | SASH1  | 6:148865872:C:G | rs75149315  | R1089Q    |
| C133       | SASH1  | 6:148867217:C:T | rs20099161  | R1139W    |
| C104       | SASH1  | 6:148869462:C:G | rs143577116 | R1171Q    |
| C115       | SERPINE1| 7:100783050:C:G | .          | R386W     |
| C43        | SP1    | 12:53776845:C:G | .          | Q372E     |
| C100       | TEK    | 9:27169568:C:G  | .          | S190L     |
| C108       | UTS2R  | 17:80332489:C:G | 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.
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). The presented data will allow the examination of 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 4). Lastly, to specifically assess the effects of maternal variants on placental function and fetal growth, 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 next restricted analysis to those cases where only a single parent had identified pathogenic variants (Table 4). 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 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 | $-0.11 \pm 0.92$ | $-0.12 \pm 1.3$ | $-0.51 \pm 1.1$ | $1.28 \pm 1.3$ |
| 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 | $0.05 \pm 0.87$ | $-0.07 \pm 1.2$ | $-0.12 \pm 1.1$ | $0.82 \pm 1.3$ |
| 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 | $-0.34 \pm 0.89$ | $-0.60 \pm 1.3$ | $-0.67 \pm 1.1$ | $1.08 \pm 1.3$ |
| P-value | 0.0153 | 0.02 | 0.01 | 0.34 |
| Was there a variant in the mother that wasn’t inherited by the infant? | Yes 47 | $0.04 \pm 0.89$ | $0.04 \pm 1.5$ | $-0.26 \pm 1.1$ | $0.86 \pm 1.4$ |
| P-value | 0.19 | 0.26 | 0.79 | 0.83 |

* Data are presented as Mean ± Standard deviation.

### 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 | $0.01 \pm 0.97$ | $-0.02 \pm 1.4$ | $-0.26 \pm 1.0$ | $1.36 \pm 0.71$ |
| P-value | 0.17 | 0.054 | 0.41 | 0.43 |
| Was there a variant in the mother that was inherited by the infant? | Yes 24 | $-0.37 \pm 0.95$ | $-0.82 \pm 1.4$ | $-0.51 \pm 1.1$ | $1.03 \pm 0.44$ |
| P-value | 0.04 | 0.59 | 0.41 | 0.43 |
| Was there a variant in the father that wasn’t inherited by the infant? | Yes 31 | $-0.04 \pm 0.85$ | $-0.22 \pm 1.1$ | $-0.18 \pm 1.1$ | $0.58 \pm 0.05$ |
| P-value | 0.97 | 0.65 | 0.48 | 0.74 |

*Data are presented as Mean ± Standard deviation.

1 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 manufacturer’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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