FGFRL1 and FGF genes are associated with height, hypertension, and osteoporosis

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Abstract

Hypertension and osteoporosis are two major disorders, which interact with each other. Specific genetic signals involving the fibroblast growth factor receptor-like 1 (FGFRL1) gene are related to high blood pressure and bone growth in giraffes. FGFRL1 is associated with cardiovascular system and bone formation. We performed an association study to investigate the role of FGFRL1 in hypertension, osteoporosis, and height determination in humans. In addition, we identified three kinds of phenotypes in fibroblast growth factor (FGF) genes and examined their association with the FGFRL1 gene. We identified 42 SNPs in the FGFRL1 gene associated with each trait. We then analyzed the potential functional annotation of each SNP. The FGFRL1 gene was found to be associated with height, hypertension, and osteoporosis, consistent with the results of a previous study. In addition, the FGF2, FGF4, FGF10, FGF18, and FGF22 genes were found to interact with the FGFRL1 gene. Our study suggests that both FGFRL1 and FGFRL1-related genes may determine the height and the prevalence of osteoporosis and hypertension in the Korean population.

Introduction

Osteoporosis is characterized by decreased bone mineral density and an increased risk of fractures, and is one of the most common chronic and metabolic bone diseases [1, 2]. Hypertension is the main risk factor for coronary heart disease, stroke, and chronic kidney disease, and is a prominent cause of death worldwide [3]. Both these diseases are metabolic conditions mediated via common pathophysiology, which means potential mechanistic links between osteoporosis and hypertension. Increasing evidence suggests that bone marrow-derived cells play a role in hypertension [4]. Osteoporosis and hypertension appear to be strongly triggered by immune cell activation, including enhanced salt intake, increased sympathetic outflow, and excessive angiotensin II and aldosterone [5]. Besides, various cohort studies reported the interplay between osteoporosis and hypertension [6–8].

A recent study identified specific genetic signals that are associated with adaptation to high blood pressure and bone growth in giraffes, with exceptional anatomy contributing to their
supplemented the information of all variants, used in the study, in the S4 Table.

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Materials and methods

Study participants

The study data were obtained from the Korean Genome and Epidemiology Study [18] Health Examinees (HEXA) study [18]. The Korean Centers for Disease and Control (KCDC) recruited 173,357 participants for the HEXA study aged 40 to 79 years from 2004 to 2013 who lived in urban (Seoul, Incheon, Daejeon, Daegu, Ulsan, Busan, and Gwangju) and rural (Gyeonggi, Sejong, Gangwon, Chungcheongbuk, Chungcheongnam, Gyeonsangbuk, Gyeonsangnam, Jeollabuk, Jeollanam, and Jeju) areas of Korea [18]. Of these, only 58,698 participants who were available single nucleotide polymorphism (SNP) information and included in the baseline study were selected for the current study. The value of body measurements with each disease are shown in S1 Table. Height [19], weight [20], diastolic blood pressure (DBP), and systolic blood pressure (SBP) were measured. Height and weight were measured using an automated measuring instrument (Dong Sahn Jenix Co., Seoul, Korea) three times for the average values. Each diastolic and systolic blood pressure was measured three times every at intervals of more than 5 minutes by a mercury sphygmomanometer in a seated position, and the average value was used. Body mass index (BMI) was computed in units of kilograms per square meter (kg/m²), using the measured height and weight values. Patients with hypertension (n = 17,086) were defined by SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, or a medical history of hypertension or use of antihypertensive medication. Controls (n = 31,440) were defined by SBP < 120 mmHg and DBP < 80 mmHg and no medical history of hypertension or anti-hypertensive drug use. The diagnosis of osteoporosis was made by a medical doctor based on bone indices measured via whole-body dual-energy X-ray absorptiometry (DXA). The final binary variable, the value we used in this study, was derived from the participants’ medical records through a questionnaire about whether there was a history of hypertension or osteoporosis. We included the patients and controls with hypertension and osteoporosis in the current study and analyzed the genetic variants associated with hypertension and osteoporosis.
of the previous diagnosis by a medical doctor. In total, after excluding 89 patients who were either non-respondents or had never been screened for osteoporosis, 55,535 controls and 3,074 cases of osteoporosis were identified.

Genotyping

Genotype data were obtained by the Center for Genome Science, Korea National Institute of Health (KNIH). DNA samples were extracted from peripheral blood and genotyping was done using the Axiom® 2.0 Reagent Kit (Affymetrix Axiom® 2.0 Assay User Guide). Genotype data were generated using the KoreanChip (KCHIP) designed by the Center for Genome Science at the KNIH. Gene location was determined in reference to the National Center for Biotechnology Information (NCBI) Human Genome Build 37 (hg19) assembly. All the gene regions analyzed in this study were expanded by 5 kb at both transcripts ends, and SNPs were selected in this range. The KCHIP has been described comprehensively in previous studies [21]. The only genotypes that satisfied these exclusion criteria: low call rate (< 0.95%), sex inconsistency, cryptic first-degree relatives, and excessive heterozygosity. SNPs with genotype call rates < 95%, Hardy–Weinberg equilibrium (HWE) \( p \)-value < \( 10^{-6} \), and minor allele frequency of < 1% were removed. A total of 465,000 variants were included after quality control. A total of 8,056,211 SNPs were used for GWAS after quality control and imputation.

Statistical analysis

PLINK version 1.90 beta (https://www.cog-genomics.org/plink2) was used for most statistical analyses. Imputation for autosomal variants was executed using IMPUTE2 with the reference panel constructed from 1000 phase 3 genomes. A logistic regression, additive genetic model was used after adjustments for age, sex, and body mass index (BMI) to investigate the association between SNPs in the \( \text{FGFRL1} \) gene and hypertension and osteoporosis. SNPs associated with height were identified via linear regression additive analysis adjusting for age and sex, with a cut-off \( p \)-value of \( P < 0.05 \). We sorted out tag SNP, the representative SNP in each genome region with high linkage disequilibrium (LD), from the haplotype block under the condition that the LD measure \( r^2 \) ≥ 0.8. Regional association plots were generated using LocusZoom (http://locuszoom.org/). The HaploReg database (https://pubs.broadinstitute.org) was used to identify functional effects, such as protein motifs, in the \( \text{FGFRL1} \) genetic variants associated with both hypertension and osteoporosis. GTExPortal databases (https://gtexportal.org) were used for expression quantitative trait loci (eQTL) analysis. RegulomeDB (https://regulomedb.org/regulome-search/) was used to rank potential functional roles. We depicted annotated gene networks using STRING database version 11.0 (https://string-db.org/) and selected the genes with direct interactions with the \( \text{FGFRL1} \) gene.

Ethical review

This study was approved by the Institutional Review Board of the Korean National Institute of Health (KNIH, KBN-2021-003) and Soonchunhyang University (202012-BR-086-01). Written informed consent was obtained from all participants.

Results

Association of the \( \text{FGFRL1} \) gene variants with height, hypertension, and osteoporosis

A total of 44 tag SNPs were identified in the \( \text{FGFRL1} \) gene. Logistic regression analysis for hypertension and osteoporosis using the additive genetic model revealed three and six
nominally significant SNPs ($P < 0.05$), respectively (Table 1). Linear regression analysis for height identified nine significant SNPs. Among nine SNPs, 3 and 6 SNPs had positive and negative associations with height, respectively (Table 1). Two SNPs (rs13143527 and rs55639339) were associated with both hypertension and osteoporosis, but none of the height-related SNPs was related to osteoporosis or hypertension. Rs55639339 showed similar patterns of increased risk for hypertension (OR: 1.043) and osteoporosis (OR: 1.087), whereas the rs13143527 variant was associated with a decreased risk of hypertension (OR: 0.967) and osteoporosis (OR: 0.939) (Table 1). A regional plot of the FGFR1 gene based on height, hypertension, and osteoporosis was drawn using LocusZoom (S1 Fig).

### Association of FGF genes with height, hypertension, and osteoporosis

The gene-gene interaction networks generated by STRING revealed connections with high confidence scores (confidence score > 0.7) between FGFR1 and five fibroblast growth factors (FGF2, FGF4, FGF10, FGF18, and FGF22) (Fig 1). The FGF10, FGF18, FGF2, FGF4, and FGF22 genes, which interact with FGFR1, were correlated with height, hypertension, and osteoporosis. Overall, SNPs related to height were the most common, and no genetic variant of the FGF4 gene was related to hypertension (S2 Table). Previous studies demonstrated an association between the FGF18 gene and height [14, 24]. Interestingly, rs8109113 in the FGF22 gene was associated with both hypertension and height, and 17 SNPs in FGF10, FGF18, and FGF2 were associated with both osteoporosis and height (Table 2).

### Functional analysis

We used the GTEx database and HaploReg to determine the biological functional annotations of the identified genetic variants and genes (Fig 2). The GTEx database was used to
obtain tissue expression data for FGFRL1. The FGFRL1 gene is expressed in various tissues, especially in the thyroid gland and arteries (Fig 2B). Rs73219733 and rs34627176, which were associated with height, were significant signals of eQTL for the FGFRL1 gene in skeletal muscle tissue ($P = 8.3 \times 10^{-5}$, $1.7 \times 10^{-12}$) (Fig 2A). In addition, motif changes were predicted for the two SNPs that were significantly correlated with hypertension and osteoporosis (S3 Table). Based on the results, the FGFRL1 gene expression varies with the SNP genotype.

**Fig 1.** Protein-protein interactions with high confidence score (confidence score $> 0.7$) for FGFRL1. Proteins in the interaction network are represented as nodes; the line color represents the type of interaction, including known interaction, predicted interaction and other types. These interactions include physical (direct) and functional (indirect) types according to computational predictions and experimental repositories.

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Table 2. Genetic variants in the FGF family associated with two of the three phenotypic traits (height, hypertension, and osteoporosis) or below the Bonferroni-corrected significance level.

| Gene   | Chr | SNP    | Minor allele | MAF | Function   | Height          | HTN            | Osteoporosis     | $p$-value |
|--------|-----|--------|--------------|-----|------------|-----------------|-----------------|------------------|-----------|
| FG2    | 4   | rs167428| C            | 0.087 | intron     | $0.112 \pm 0.054$ | 0.037           | 1.040 (0.99–1.09) | 0.122     |
|        | 4   | rs308387| A            | 0.052 | intron     | $0.234 \pm 0.068$ | $5.85 \times 10^{-4}$ | 1.023 (0.96–1.09) | 0.487     |
| FG4    | 11  | rs58166091| A            | 0.213 | -          | $0.114 \pm 0.037$ | $2.16 \times 10^{-3}$ | 0.989 (0.96–1.02) | 0.544     |
| FG10   | 5   | rs1727836| C            | 0.054 | intron     | $-0.161 \pm 0.067$ | $0.016$         | 0.993 (0.93–1.06) | 0.816     |
|        | 5   | rs13154419| G            | 0.412 | intron     | $0.112 \pm 0.031$ | $2.89 \times 10^{-4}$ | 0.991 (0.96–1.02) | 0.545     |
|        | 5   | rs1448039| A            | 0.500 | intron     | $-0.094 \pm 0.030$ | $1.90 \times 10^{-3}$ | 1.006 (0.98–1.04) | 0.653     |
| FG18   | 5   | rs10463007| T            | 0.404 | -          | $0.081 \pm 0.031$ | $9.26 \times 10^{-3}$ | 0.990 (0.96–1.02) | 0.498     |
| FG22   | 19  | rs8109113| G            | 0.024 | intron     | $-0.241 \pm 0.100$ | $0.016$         | 0.901 (0.82–0.99) | $0.028$ |

Age, sex and body mass index (BMI) were included as covariant in all genetic models. Findings with $P < 0.05$ are indicated in bold. The $p$-values which satisfied the Bonferroni-corrected significance level regarding each gene are indicated in bold and underlined. Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; HTN, hypertension; $\beta$, regression coefficient; s.e, standard error; OR, odds ratio; CI, confidence interval.

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Discussion

Our study validated the correlation between FGFRL1 gene and height, hypertension, and osteoporosis. The results are consistent with a previous study that suggested an association of FGFRL1 with the cardiovascular and skeletal systems [10, 12]. We identified 16 SNPs in the FGFRL1 gene that were associated with the traits of interest. We then annotated the potential biological function of these SNPs. Similarly, the FGF2, FGF4, FGF10, FGF18, and FGF22 genes, which showed interactions with the FGFRL1 gene, were associated with height, hypertension, and osteoporosis.

Most previous genetic association studies analyzed the association of FGFRL1 with bone formation or bone density, and seldom with hypertension. In the present study, two SNPs were identified with significant ($P < 0.05$) association with both osteoporosis and hypertension: the minor allele of rs55639339 was associated with an increased risk of both diseases, while the minor allele of rs10010999 lowered the risk of both diseases, indicating a similar trend in prevalence of both diseases involving each genetic variant. Thus, our results are consistent with previous findings suggesting that osteoporosis is associated with metabolic diseases including hypertension [22]. Meanwhile, FGFRL1 is known to be essential for vasculogenesis and ventricular septation. Indeed, Fgfrl1-/- embryos manifested defects in ventricular septation and congenital heart defects [10]. Additionally, a functional study in zebrafish revealed a significant role of Fgfrl1 during gill cartilage development and craniofacial skeletogenesis [23–25]. Accordingly, the results of this replication study, which indicate that the genetic differences influence the risk of osteoporosis and hypertension, provide insight into the role of the FGFRL1 gene while supporting previous functional studies.

It is well documented that the FGE/FGFR signaling axis plays an essential role in development, tissue homeostasis, and metabolism [26, 27]. Mutations and SNPs of FGFs are known...
associated with multiple skeletal disorders [14]. For instance, a constitutionally increased expression of the FGF4 gene is a risk factor for craniosynostosis [27]. Overexpression of FGF2 in mice resulted in shortened long bones along with defective mineralization and osteopenia, suggesting that the gene acts as a negative regulator of bone formation [28, 29]. Also, the genetic knockdown of FGF10 is related to skeletal phenotypes such as craniosynostosis in a mouse model [30], and FGF18 is expressed during osteoblast differentiation [31]. Indeed, the present study revealed significant genetic signals in FGF2, FGF10, and FGF18 associated with height (S4 Table). Furthermore, several SNPs in FGF18 were associated with osteoporosis (S2 Table).

By contrast, genetic variants in FGF2 also showed an association with hypertension. FGF2 is widely expressed in the myocardium, coronary vessels, and smooth muscle cells of the aorta [32, 33]. Besides, FGF2 knock-out mice exhibit reduced vascular tension and decreased arterial blood pressure, suggesting autonomic dysfunction [34, 35]. Interestingly, all of the SNPs in FGF2 that were associated with hypertension suggested that the risk of hypertension was diminished with minor alleles (S2 Table). These results presented that the FGFRL1 signaling pathway could be considered in cardiovascular disease and hypertension in humans, suggesting that the variations in the FGF2 gene implicate the heart or vascular tone.

Due to the absence of the intracellular tyrosine kinase domain in FGFRL1, which is essential for downstream FGF signaling, FGFRL1 is widely assumed to act as a decoy receptor (competitive inhibitor) that joins and regulates FGF ligands [11, 36, 37]. Interaction between FGF and FGFRs is known to mediate several developmental phenomena, such as differentiation of mesenchymal stromal cells (MSCs) [38–40]. Kahkonen et al. showed that FGFRL1 mRNA expression is remarkably increased during differentiation of MSCs into osteoblasts and adipocyte differentiation, and silencing of FGFRI and FGFRII in MSCs decreased the FGFRL1 expression in osteoblasts and adipocytes [20]. The discovery that FGFRI and FGFRII modulate FGFRL1 expression in MSCs highlighted the role of FGFRL1 in MSC differentiation into osteoblasts and adipocytes [20]. Thus, consistent with studies associating genetic signals of the FGFRL1 gene, FGF, and FGF families, our results (gene-gene interaction network (Fig 1) and association test (Tables 1 and 2)) suggested that the interaction between FGFRL1 and FGF family affects the cardiovascular and skeletal systems.

However, our study has several limitations. First, except for hypertension, none of the continuous variables (distal radius speed of sound (DR-SOS), midshaft tibia speed of sound (MT-SOS), and T score) related to osteoporosis were identified only depending on the medical history. Second, although lifestyle and comorbidities definitely influence the risk of hypertension and osteoporosis, we did not evaluate them in the present study. Further studies are needed to evaluate additional factors including gender, lifestyle, and co-morbid conditions.

In conclusion, we have replicated the association between FGFRL1 and height, hypertension, and osteoporosis in the Korean population, and found genetic variants associated with each trait. The genetic variants in the FGF family members that interact with FGFRL1 were associated with height, hypertension, and osteoporosis. The findings suggest that the giraffe-specific FGFRL1 gene, which is associated with biological characteristics in giraffes, including tall stature and cardiovascular adaptations, is related to the corresponding phenotype in humans. Thus, our study provides an approach to the genetic basis of the pleiotropic effect of FGF/FGFR signaling.

**Supporting information**

**S1 Fig. Regional association plot of the FGFRL1 genetic variants.** Signals related to (a) height, (b) hypertension and (c) osteoporosis in the FGFRL1 gene are plotted as -log₁₀ P-
values. The color of each SNP plot shows its linkage disequilibrium (LD) (using $r^2$ values) with the novel SNP (purple diamond) within the association locus. The y-axis on the right shows the recombination rate according to the HapMap database. The above image was constructed using the LocusZoom program (http://locuszoom.org/).

**S1 Table.** Characteristics of the subjects in the HEXA study.

**S2 Table.** Genetic variants in *FGF* family members associated with height, hypertension and osteoporosis.

**S3 Table.** HaploReg results of genetic variants in *FGFRL1* that were associated with both hypertension and osteoporosis. Abbreviations: A1, minor allele; A2, major allele. The lower the Regulome DB score, the greater the effect on SNP.

**S4 Table.** Association of all genetic variants in *FGFRL1* and *FGF* family members with height, hypertension, and osteoporosis. Age, sex and body mass index (BMI) were included as covariant in all genetic models. SNPs associated with both hypertension and osteoporosis in common and had $P < 0.05$ are indicated in bold. The $p$-values which are satisfied the Bonferroni-corrected significance level regarding each gene are indicated in bold and underlined.

**Author Contributions**

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**References**

1. Zhou J, Zhang Q, Yuan X, Wang J, Li C, Sheng H, et al. Association between metabolic syndrome and osteoporosis: a meta-analysis. Bone. 2013; 57: 30–35. https://doi.org/10.1016/j.bone.2013.07.013

   PMID: 23871747
2. Al-Hariri M, Aldhafery B. Association of Hypertension and Lipid Profile with Osteoporosis. Scientifica. 2020; 2020. https://doi.org/10.1155/2020/7075815 PMID: 32765925

3. Burnier M, Egan BM. Adherence in hypertension: a review of prevalence, risk factors, impact, and management. Circ Res. 2019; 124: 1124–1140. https://doi.org/10.1161/CIRCRESAHA.118.313220 PMID: 30920917

4. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, et al. Role of the T cell in the genesis of angiotensin II–induced hypertension and vascular dysfunction. Exp Med. 2007; 204: 2449–2460. https://doi.org/10.1084/jem.20070657 PMID: 17875676

5. Do Carmo L, Harrison DG. Hypertension and Osteoporosis: Common Pathophysiological Mechanisms. Medicine in Novel Technology and Devices. 2020: 100047. https://doi.org/10.1016/j.medntd.2020.100047

6. Chai H, Ge J, Li L, Li J, Ye Y. Hypertension is associated with osteoporosis: a case-control study in Chinese postmenopausal women. BMC Musculoskelet Disord. 2021; 22: 1–7. https://doi.org/10.1186/s12891-021-04124-9

7. Lin HH, Huang CY, Hwang LC. Association between metabolic syndrome and osteoporosis in Taiwanese middle-aged and elderly participants. Arch Osteoporos. 2018; 13: 1–7. https://doi.org/10.1007/s11657-018-0467-z PMID: 29705875

8. Li C, Zeng Y, Tao L, Liu S, Ni Z, Huang Q, et al. Meta-analysis of hypertension and osteoporotic fracture risk in women and men. Osteoporos Int. 2017; 28: 2309–2318. https://doi.org/10.1007/s00198-017-4050-z PMID: 28447105

9. Liu C, Gao J, Cui X, Li Z, Chen L, Yuan Y, et al. A towering genome: Experimentally validated adaptations to high blood pressure and extreme stature in the giraffe. Sci Adv. 2021; 7: eabe9459. https://doi.org/10.1126/sciadv.abe9459 PMID: 33731352

10. Trueb B. Biology of FGFR1, the fifth fibroblast growth factor receptor. Cell Mol Life Sci. 2011; 68: 951–964. https://doi.org/10.1007/s00018-010-0576-3 PMID: 21080029

11. Morris JA, Kemp JP, Yootlen SE, Laurent L, Logan JG, Chai RC, et al. An atlas of genetic influences on osteoporosis in humans and mice. Nat Genet. 2019; 51: 258–266. https://doi.org/10.1038/s41588-018-0302-x PMID: 30598549

12. Rieckmann T, Zhuang L, Flück CE, Trueb B. Characterization of the first FGFR1 mutation identified in a craniosynostosis patient. Biophys Acta Mol Basis. 2009; 1792: 112–121. https://doi.org/10.1016/j.bbadis.2008.11.006 PMID: 19056490

13. Kichaev G, Bhatia G, Loh PR, Gazal S, Burch K, Freund MK, et al. Leveraging polygenic functional enrichment to improve GWAS power. Am J Hum Genet. 2019; 104: 65–75. https://doi.org/10.1016/j.ajhg.2018.11.008 PMID: 30593570

14. Kim SK. Identification of 613 new loci associated with heel bone mineral density and a polygenic risk score for bone mineral density, osteoporosis and fracture. PLoS One. 2018; 13: e0200785. https://doi.org/10.1371/journal.pone.0200785 PMID: 30048462

15. Mahajan A, Talluun D, Thurner M, Robertson NR, Torres JM, Rayner NW, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet. 2018; 50: 1505–1513. https://doi.org/10.1038/s41588-018-0241-6 PMID: 30297969

16. Agaba M, Ishengoma E, Miller WC, McGrath BC, Hudson CN, Reina OCB, et al. Giraffe genome sequence reveals clues to its unique morphology and physiology. Nat Commun. 2016; 7: 1–8. https://doi.org/10.1038/ncomms11519 PMID: 27187213

17. Kim K, Han BG, group TK. Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium. International Journal of Epidemiology. 2016; 46: e20–e. https://doi.org/10.1093/ije/dyy316 PMID: 27085081

18. Zubakov D, Liu F, Van Zelm M, Vermeulen J, Oostra B, Van Duijn C, et al. Estimating human age from T-cell DNA rearrangements. Curr Biol. 2010; 20: 970–971. https://doi.org/10.1016/j.cub.2010.02.022 PMID: 21093786

19. Kähkönen T, Ivaska K, Jiang M, Bükö K, Väänänen H, Härkönen P. Role of fibroblast growth factor receptors (FGFR) and FGFR-like1 (FGFRL1) in mesenchymal stromal cell differentiation to osteoblasts and adipocytes. Mol Cell Endocrinol. 2018; 461: 194–204. https://doi.org/10.1016/j.mce.2017.09.015 PMID: 28923346
22. Chin KY, Chan CY, Subramaniam S, Muhammad N, Fairs A, Ng PY, et al. Positive association between metabolic syndrome and bone mineral density among Malaysians. Int J Med Sci. 2020; 17: 2585. https://doi.org/10.7150/ijms.49030 PMID: 33029101

23. Hall C, Flores MV, Murison G, Crosier K, Crosier P. An essential role for zebrafish Fgfrl1 during gill cartilage development. Mech Dev. 2006; 123: 925–940. https://doi.org/10.1016/j.mod.2006.08.006 PMID: 17011755

24. Hogan BM, Hunter MP, Oates AC, Crowhurst MO, Hall NE, Heath JK, et al. Zebrafish gcm2 is required for gill filament budding from pharyngeal ectoderm. Dev Biol. 2004; 276: 508–522. https://doi.org/10.1016/j.ydbio.2004.05.011 PMID: 15327784

25. Hanaoka R, Ohmori Y, Uyemura K, Hosoya T, Hotta Y, Shirao T, et al. Zebrafish gcmb is required for pharyngeal cartilage formation. Mech Dev. 2004; 121: 1235–1247. https://doi.org/10.1016/j.mod.2004.05.011 PMID: 15327784

26. Xie Y, Su N, Yang J, Tan Q, Huang S, Jin M, et al. FGF/FGFR signaling in health and disease. Signal Transduct Target Ther. 2020; 5: 1–38. https://doi.org/10.1038/s41392-020-00222-7

27. Grillo L, Greco D, Pettinato R, Avola E, Potenza N, Castiglia L, et al. Increased FGF3 and FGF4 gene dosage is a risk factor for craniosynostosis. Gene. 2014; 534: 435–439. https://doi.org/10.1016/j.gene.2013.09.120 PMID: 24120895

28. Coffin JD, Florkiewicz RZ, Neumann J, Mort-Hopkins T, Dorn 2nd G, Lightfoot P, et al. Abnormal bone growth and selective translational regulation in basic fibroblast growth factor (FGF-2) transgenic mice. Mol Biol Cell. 1995; 6: 1861–1873. https://doi.org/10.1091/mbc.6.12.1861 PMID: 8590811

29. Sobue T, Naganawa T, Xiao L, Okada Y, Tanaka Y, Ito M, et al. Over-expression of fibroblast growth factor-2 causes defective bone mineralization and osteopenia in transgenic mice. J Cell Biochem. 2005; 95: 83–94. https://doi.org/10.1002/jcb.20389 PMID: 15723277

30. Hajihosseini MK, Duarte R, Pegrum J, Donjacour A, Lana-Elola E, Rice DP, et al. Evidence that Fgf10 contributes to the skeletal and visceral defects of an Apert syndrome mouse model. Dev Dyn. 2009; 238: 376–385. https://doi.org/10.1002/dvdy.21648 PMID: 18773495

31. Ornitz DM, Marie PJ. Fibroblast growth factors in skeletal development. Curr Top Dev Biol. 2019; 133: 195–234. https://doi.org/10.1016/bs.ctdb.2018.11.020 PMID: 30902253

32. Liao S, Bodmer J, Pietras D, Azhar M, Doetschman T, Schultz JEJ. Biological functions of the low and high molecular weight protein isoforms of fibroblast growth factor-2 in cardiovascular development and disease. Dev Dyn. 2009; 238: 249–264. https://doi.org/10.1002/dvdy.21677 PMID: 18773489

33. House SL, House BE, Glascock B, Kimball T, Nusayr E, Schultz JEJ, et al. Fibroblast growth factor 2 mediates isoproterenol-induced cardiac hypertrophy through activation of the extracellular regulated kinase. Mol Cell Pharmacol. 2010; 2: 143. https://doi.org/10.4255/mcpharmacol.10.20 PMID: 21274419

34. Zhou M, Sutliff RL, Paul RJ, Lorenz JN, Haudenschild CC, et al. Fibroblast growth factor 2 control of vascular tone. Nat Med. 1998; 4: 201–207. https://doi.org/10.1038/nm0298-201 PMID: 9461194

35. Dono R, Texido G, Dussel R, Ehmke H, Zeller R. Impaired cerebral cortex development and blood pressure regulation in FGF-2-deficient mice. EMBO J. 1998; 17: 4213–4225. https://doi.org/10.1093/emboj/17.15.4213 PMID: 9687490

36. Sleeman M, Fraser J, McDonald M, Yuan S, White D, Grandison P, et al. Identification of a new fibroblast growth factor receptor, FGFR5. Gene. 2001; 271: 171–182. https://doi.org/10.1016/s0378-1119(01)00518-2 PMID: 11418238

37. Trueb B, Zhuang L, Taeschler S, Wiedemann M. Characterization of FGFR1, a novel fibroblast growth factor (FGF) receptor preferentially expressed in skeletal tissues. J Biol Chem. 2003; 278: 33857–33865. https://doi.org/10.1074/jbc.M300281200 PMID: 12813049

38. Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. Nat Rev Drug Discov. 2009; 8: 235–253. https://doi.org/10.1038/nrd2792 PMID: 19247306

39. Ornitz DM, Itoh N. The FGF family: biology, pathophysiology and therapy. Nat Rev Drug Discov. 2009; 8: 235–253. https://doi.org/10.1038/nrd2792 PMID: 19247306

40. Du X, Xie Y, Xian CJ, Chen L. Role of FGFs/FGFRs in skeletal development and bone regeneration. J Cell Physiol. 2012; 227: 3731–3743. https://doi.org/10.1002/jcp.24083 PMID: 22378383