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Wnt Signaling Associated Human Diseases

Yanqin Lu[1,2]*, Xiuzhi Ren[3], Yanzhou Wang[4] and Jinxiang Han[1,2]

[1]*Key Laboratory for Biotech-Drugs Ministry of Health, Key Laboratory for Rare & Uncommon Diseases of Shandong Province, Shandong Medicinal Biotechnology Centre, Shandong Academy of Medical Sciences, Jinan, China*

[2]*School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, China*

[3]*Department of Orthopedic Surgery, The People's Hospital of Wuqing District, China*

[4]*Department of Pediatric Surgery, Shandong Provincial Hospital, China*

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***Corresponding author:** Yanqin Lu, Shandong Academy of Medical Sciences, #18877 Jingshi Road, Jinan 250062, China, Email: yanqinlu@yahoo.com

Abstract

Wnts and their signaling cascades regulate a wide variety of biological processes and diseases. Aberrant canonical and non-canonical Wnt signaling components are pathogenic to various human genetic diseases and non-genetic diseases. Here, we review the spectrum of human diseases related with Wnt ligands, receptor, co-receptor, agonists, antagonists, transcript factor and other components in the signaling pathways. Results show that diseases related by Wnt signaling are predominated by genetic diseases, especially genetic skeletal disorders.

Keywords: Wnt Singaling Components; Genetic Skeletal Disorders; Non-Genetic Diseases

Abbreviations: Fzd: Frizzled; CK1: Casein kinase-1; GSK-3β: Glycogen synthase kinase-3β; APC APC: Adenomatous polyposis coli; TCF/LEF: T-cell factor/lymphoid enhancer factor; PCP: Planar cell polarity; Dsh/Dvl: Dishvelled; Pk: Prickle; DKK: Dickkopf; WIF: Wnt inhibitory factor; BMD: Bone Mass Density

Wnt Signaling Pathways

Wnt are secreted lipid-modified glycoproteins including 19 family members that transduces signal through one more of different signaling pathways. Wnt ligand binds to serial Frizzled (Fzd) receptor and LRP5/6 co-receptor, then destroy the destruction complex consisting of β-catenin, axin, casein kinase-1 (CK1), glycogen synthase kinase-3β (GSK-3β) and the adenomatous polyposis coli (APC). This leads to the translocation of β-catenin to the nucleus, where it binds to transcriptional factors T-cell factor/lymphoid enhancer factor (TCF/LEF) to induce the transcription of Wnt target genes. β-catenin-independent Wnt signaling pathways are multiple, Wnt/ planar cell polarity (PCP) pathway, utilizing small Rho-like GTPases, is related with polarization information for guiding tissue patterning and morphogenesis [1-5]. PCP is composed of core protein complexes and Fat/Daschsous (Ds)/Fj (Four-jointed) group. The core protein complexes include Frizzled, Flamingo (Fmi/Celsr), Van Gogh (Drosophila Vang or Stb/mammalian Vang), Dishvelled (Dsh/Dvl), Diego, and Prickle (Pk) [5-10]. Wnt/Ca2+ pathway, modulating intracellular Ca2+ level through Wnt5a and Fzd2-6 receptor as well as Ror1/2 co-receptor, as well as coreceptor Ror1/2 [11-15]. These signaling pathways are regulated by antagonists/agonists include secreted Frizzled related protein (SRFP) ,Dickkopf (DKK) family, Wnt inhibitory factor (WIF)1, sclerostin, Wntless, R-Spondin, and norrin. Wnt signaling pathway is vital to various biological processes, there's no doubt that gene mutations of Wnt signaling cascades are causative to multiple human diseases.

Wnt Signaling and Human Diseases

Table 1: Human diseases associated with components of Wnt signaling pathway.

Diseases	MIM number	Inheritance	Gene	Reference
Osteogenesis imperfecta, type XV	615220	AR	WNT1	Pyott et al. [5].
Osteoporosis, early-onset, susceptibility to, autosomal dominant	615221		WNT1	Laine et al. [6].
Autism	611015		wnt2	Wassink et al. [7].

Tetra-amelia syndrome 1	273395	AR	Wnt3	Niemann et al. [8].
SERKAL syndrome	611812	AR	Wnt4	Mandel et al. [9].
Mullerian aplasia and hyperandrogenism	158330	AD	Wnt4	Biason-Lauber et al. [10].
Robinow syndrome, autosomal dominant 1	180700	AD	Wnt5a	Person et al. [11].
type 2 diabetes	125853		Wnt5b	Kanazawa et al. [12].
Fuhrmann syndrome	228930	AR	Wnt7a	Woods et al. [13].
Ulna and fibula, absence of, with severe limb deficiency	276820	AR	Wnt7a	Woods et al. [13].
Odontoonychodermal dysplasia	257980	AR	Wnt10a	Adaimy et al. [14].
Schopf-Schulz-Passage syndrome	224750	AR	Wnt10a	Bohring et al. [15].
Tooth agenesis, selective, 4	150400	AR, AD	Wnt10a	Kantaputra et al. [16].
Split-hand/foot malformation 6	225300	AR	Wnt10b	Ugur et al. [17].
Tooth agenesis, selective, 8	617073	AD	Wnt10b	Yu et al. [18].
Myasthenic syndrome, congenital, 17	616304	AR	LRP4	Ohkawara et al. [19].
Cenani-Lenz syndactyly syndrome	212780	AR	LRP4	Li et al. [20].
Sclerosteosis 2	614305	AR, AD	LRP4	Leupin et al. [21].
Exudative vitreoretinopathy 4	601813	AD, AR	LRP5	Toomes et al. [22].
Osteopetrosis, autosomal dominant 1	607634	AD	LRP5	Van Wesenbeeck et al. [23], Van Hul et al. [24].
Osteoporosis-pseudoglioma syndrome	259770	AR	LRP5	Gong et al. [25].
Osteosclerosis	144750	AD	LRP5	Van Wesenbeeck et al. [23].
Hyperostosis, endosteal	144750	AD	LRP5	Van Wesenbeeck et al. [23].
Polycystic liver disease 4 with or without kidney cysts	617875	AD	LRP5	Cnossen et al. [26].
van Buchem disease, type 2	607636	AD	LRP5	Van Wesenbeeck et al. [23]. Little et al. [27].
Bone mineral density variability 1	601884	AD	LRP5	Nguyen et al. [28].
Osteoporosis	166710	AD	LRP5	Estrada et al. [29].
Tooth agenesis, selective, 7	616724	AD	LRP6	Massink et al. [30].
Coronary artery disease, autosomal dominant, 2	610947	AD	LRP6	Mani et al. [31].
Myocardial infarction, susceptibility to	608446		LRP8	Shen et al. [32].
Robinow syndrome		AR	FZD2	White et al. [33].
Retinopathy of prematurity	133780	AD	FZD4	MacDonald et al. [34].
Exudative vitreoretinopathy 1	133780	AD	FZD4	Robitaille et al. [35].
receptor wnt5a			FZD5	
Nail disorder, nonsyndromic congenital, 10, claw-shaped nails	614157	AR	FZD6	Frojmark et al. [36].
Williams syndrome			FZD9	Wang et al. [37].
Fetal akinesia deformation sequence	208150	AR	MUSK	Tan-Sindhunata et al. [38].
Myasthenic syndrome, congenital, 9, associated with acetylcholine receptor deficiency	616325	AR	MUSK	Chevessier et al. [39].
Obesity, association with	601665	Mu, AR, AD	SDC3	Ha et al. [40].
Deafness, autosomal recessive 108	617654	AR	ROR1	Diaz-Horta et al. [41].
Brachydactyly, type B1	113000	AD	ROR2	Oldridge et al. [42].
Robinow syndrome, autosomal recessive	268310	AR	ROR2	van Bokhoven et al. [43]. Afzal et al. [44].
Simpson-Golabi-Behmel syndrome, type 1	312870	XLR	GPC3	Pilia et al. [45].
Wilms tumor, somatic	194070		GPC3	White et al. [46].
Omodysplasia 1	258315	AR	GPC6	Campos-Xavier et al. [47].
Osteoarthritis susceptibility 1	165720	Mu	SFRP3	Loughlin Eet al. [48].
Pyle disease	265900	AR	SFRP4	Kiper et al. [49].
Craniodiaphyseal dysplasia, autosomal dominant	122860	AD	SOST	Kim et al. [50].

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Sclerosteosis 1	269500	AR	SOST	Brunkow et al. [51].
Van Buchem disease	239100	AR	SOST	Balemans et al. [52].
Ectodermal dysplasia 13, hair/tooth type	617392	AR	KREMEN1	Issa et al. [53].
Tooth Agenesis		AD	DKK1	Dincka et al. [54].
Palmoplantar hyperkeratosis with squamous cell carcinoma of skin and sex reversal	610644	AR	RSPO1	Parma [55].
Palmoplantar hyperkeratosis and true hermaphroditism	610644	AR	RSPO1	Tomaselli et al. [56].
Humerofemoral hypoplasia with radiotibial ray deficiency	618022		RSPO2	Szenker-Ravi et al. [57].
Tetraamelia syndrome 2	618021		RSPO2	Szenker-Ravi et al. [57].
Anonychia congenita	206800	AR	RSPO4	Blaydon et al. [58].
Exudative vitreoretinopathy 2, X-linked	305390		NDP	Chen et al. [59].
Norrie disease	310600	XLR	NDP	Schuback et al. [60].
Bone mineral density, low, susceptibility to	615311		LGR4	Styrkarsdottir et al. [61].
Sessile serrated polyposis cancer syndrome	617108	AD	RNF43	Gala et al. [62].
Robinow syndrome, autosomal dominant 2	616331	AD	DVL1	White et al. [63].
Robinow syndrome, autosomal dominant 3	616894	AD	DVL3	White et al. [64].
Caudal duplication anomaly	607864		AXIN1	Oates et al. [65].
Hepatocellular carcinoma, somatic	114550		AXIN1	Taniguchi et al. [66].
Colorectal cancer, somatic	114500		AXIN2	Fearnhead et al. [67].
Oligodontia-colorectal cancer syndrome	608615	AD	AXIN2	Lammi et al. [68].
Colorectal cancer, somatic	114500		CTNNB1	Morin et al. [69].
Exudative vitreoretinopathy 7	617572	AD	CTNNB1	Panagiotou et al. [70].
Hepatocellular carcinoma, somatic	114550		CTNNB1	Koch et al. [71]. Chan et al. [72].
Medulloblastoma, somatic	155255		CTNNB1	Pugh et al. [73].
Mental retardation, autosomal dominant 19	615075	AD	CTNNB1	Tucci et al. [74].
Ovarian cancer, somatic	167000		CTNNB1	Sagae et al. [75].
Pilomatricoma, somatic	132600		CTNNB1	Chan et al. [72].
Arrhythmogenic right ventricular dysplasia 12	611528	AD	JUP	Asimaki et al. [76].
Naxos disease	601214	AR	JUP	McKoy et al. Cabral et al. [77].
Adenomatous polyposis coli	175100	AD	APC	Groden et al. [78].
Brain tumor-polyposis syndrome 2	175100	AD	APC	Hamilton et al. [79].
Gardner syndrome	175100	AD	APC	Bapat et al. [80].
Colorectal cancer, somatic	114500		APC	Nishisho et al. [81].
Desmoid disease, hereditary	135290	AD	APC	Scott et al. [82].
Gastric cancer, somatic	613659		APC	Horii et al. [83].
Hepatoblastoma, somatic	114550		APC	Su et al. [84].
Sotos syndrome 3	617169	AR	APC2	Almuriekhi et al. [85].
Advanced sleep-phase syndrome, familial, 2	615224	AD	CSNK1D	Xu et al. [86].
Sebaceous tumors, somatic			LEF1	Takeda et al. [87].
Agammaglobulinemia 8, autosomal dominant	616941	AD	TCF3	Boisson et al. [88].
Corneal dystrophy, Fuchs endothelial, 3	613267	AD	TCF4	Soliman et al. [89].
Pitt-Hopkins syndrome	610954	AD	TCF4	Amiel et al. Zweier et al. [90].
Anauxetic dysplasia 2	617396	AR	POP1	Glazov et al. [91].
ZTTK syndrome	617140	AD	SON	Zhu et al. [92].
Focal dermal hypoplasia	305600	XLD	PORCN	Wang et al. [93].

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As shown in Table 1. spectrum of human diseases related with Wnt signaling is broad, ranging from genetic diseases to complex diseases, but mainly for genetic diseases. Pathogenic genes for diseases are involved in the various Wnt ligands, receptor/co-receptor and regulators. The majority of gene mutations cause genetic diseases, in which genetic skeletal disorders are the main form [16-25].

Wnt Signaling and Human Skeletal Disorders

Components of Wnt signaling have been identified to have close relationship with high or low bone density. LRP5 has both loss or gain of function mutations that leads to low bone mass diseases including osteopetrosis (mim 607634, 166710) and osteoporosis-pseudoglioma syndrome (259770) [26-30]. high bone mass diseases of osteosclerosis/ hyperostosis, endosteal (mim 144750, Bone mineral density variability 1 (mim 601884) and van Buchem disease, type 2 (mim 607636). Sclerosteosis (SOST) mutation cause the high bone mass density (BMD) diseases of Van Buchem syndrome (mim 239100), sclerosteosis 1 (mim 269500) and craniodiaphyseal dysplasia (mim 122860) [31-35]. LRP4 mutation leads to type I sclerosteosis (mim 614305), which is also the disease with high BMD. Wnt1 is the pathogenic gene for type XV osteogenesis imperfect, and heterozygous of it mutation is responsible for early-onset osteoporosis. Nonsense variation of c.376C-T in LGR4, is strongly associated with low bone mass density and osteoporotic fractures. SFRP3 as the antagonist of Wnt signaling, is one of the susceptibility gene for osteoarthritis. Wnt5a (phenotype mim 180700) [36-40]. Fzd2, Ror2 (phenotype mim 268310), DVL1/3 (phenotype mim 616331, 616894) genes are all pathogenic genes for different Robinow syndrome types, which is highly related with Wnt/PCP signaling pathway. Wnt3 and Wnt7a are required for normal limb development and patterning [41-45].

Mutation of them leads to aberrant limb disorder (phenotype omim 273395, 276820, 228930). LRP4 (phenotype omim 212780) [46-55]. GPC6 (phenotype omim 258315) and SFRP4 (phenotype omim 265900) are all pathogenic gens for limb disorders. Furthermore, Homozygous mutation of RSPO2 is reported to cause humerofemoral hypoplasia with radiotibial ray deficiency [56-65]. (mim 618022) and tetraamelia syndrome 2 (mim 618021). Wnt10a/b are required for normal tooth development. Mutation of Wnt10a/b (phenotype mim 224750, 257980, 150400, 617073) and LRP6 receptor [66-75]. (phenotype mim 603507), modulator of DKK1, KREMEN1 (phenotype mim 617392) and AXIN2 (phenotype mim 608615) are all causative to tooth agenesis and these genes are involved in canonical Wnt signaling. Meanwhile, receptor Fzd6 and agonist RSPO1/4 mutations of Wnt signaling are related with nail disorder such as claw-shaped [76-85]. nails (mim 614157), palmoplantar hyperkeratosis (mim 610644), anonychia congenital (mim 206800). Wnt 10b and ROR2, GP3 receptors in the Wnt signaling is involved in the diseases of foot malformation ectrodactyly (mim 225300), brachydactyly B1(mim 113000) and Simpson-Golabi-Behmel syndrome (mim 312870) [86].

Wnt Signaling and Non-Human Skeletal Disorders

Wnt signaling is implicated in various non-skeletal genetic disorders. Neurological diseases associated with Wnt signaling include Pitt-Hopkins syndrome (mim 610954), Sotos syndrome 3(mim 617169), mental retardation (mim 615075) and ZTTK syndrome (mim 617140), with pathogenic gene of TCF4, APC2, CTNNB1 and Son, respectively. Mutation of FZD4, NDP, LRP5 and CTNNB1 cause different type of exudative vitreoretinopathy (mim 133780, 305390, 601813, 617572) [87-90]. APC and RNF43 are pathogenic genes for brain tumor-polyposis syndrome (mim 175100) and sessile serrated polyposis cancer syndrome (mim 617108) correspondingly [91]. LRP6 and JUP gene are responsible for coronary artery disease (mim 610947), Naxos disease (mim 601214) and arrhythmogenic right ventricular dysplasia (mim 6115280). Wnt signaling is associated with wide spectrum of complex diseases, such as autism [92,93]. obesity, myocardial infarction, especially different types of cancers, with APC, CTNNB1, AXIN1/2, LEF1 and GPC3 from Wnt signaling cascades. Hence, various drugs have been implicated in the treatment of different cancers.

Conclusion

The review focuses on the relationship between Wnt signaling components and human diseases. Genetic and phenotypic heterogeneity is observed in both canonical and non-canonical Wnt signaling pathways. Skeletal dysplasia and cancers are the main types of Wnt signaling related diseases. The diseases of Wnt signaling preference provides the targets for treatment. Nowadays, many drugs targeting Wnt signaling is in preclinical or clinical periods for cancer, osteoporosis, neurodegenerative disease. Hopefully, the therapeutic of Wnt signaling related diseases will be successful in the future.

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References

1. Vander Vorst K, Hatakeyama J, Berg A, Lee H, Carraway KL (2018) Cellular and molecular mechanisms underlying planar cell polarity pathway contributions to cancer malignancy, Semin Cell Dev Biol 81: 78-87.

2. Humphries AC, Mlodzik M (2018) Wnt/PCP signaling in development and cancer, Curr Opin Cell Biol 51: 110-116.

3. Kuhl M, Sheldahl LC, Malbon CC, Moon RT (2000) Ca^{2+}/Calmodulin-dependent Protein Kinase II Is Stimulated by Wnt and Frizzled Homologs and Promotes Ventral Cell Fates in Xenopus* J Biol Chem 275(17): 12701-12711.

4. Kengaku M, Capdevila J, Rodriguez Esteban C, De La Pena J, Johnson RL, et al. (1998) Distinct WNT pathways regulating AER formation and dorsoventral polarity in the chick limb bud Science 280(5367): 1274-1277.

5. Pyott SM, Tran TT, Leistritz DF, Pepin MG, Mendelsohn NJ, et al. (2013) WNT1 mutations in families affected by moderately severe and

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progressive recessive osteogenesis imperfecta Am J Hum Genet 92(4): 590-597.

6. Laine CM, Joeng KS, Campeau PM, Kiviranta R, Tarkkonen K, et al. (2013) WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta. N Engl J Med 368(19): 1809-1816.

7. Wassink TH, Piven J, Vieland VJ, Huang J, Swiderski RE, et al. (2001) Evidence supporting WNT2 as an autism susceptibility gene. Am J Med Genet 105(5): 406-413.

8. Niemann S, Zhao C, Pascu F, Stahl U, Aulepp U, et al. (2004) Am J Hum Genet 74(3): 558-563

9. Mandel H, Shemer R, Borochowitz ZU, Okopnik M, Knopf C, (2008) Am J Hum Genet 82(1): 39-47.

10. Biason Lauber A, Konrad D, Navratil F, Schoenle EJ (2004) A WNT4 mutation associated with Müllerian-duct regression and virilization in a 46,XX woman. N Engl J Med 351(8): 792-798.

11. Person AD, Beiraghi S, Sieben CM, Hermanson S, Neumann AN, et al. (2010) WNT5A mutations in patients with autosomal dominant Robinow syndrome. Dev Dyn 239(1): 327-337.

12. Kanazawa A, Tsukada S, Sekine A, Tsunoda T, Takahashi A, et al. (2004) Association of the Gene Encoding Wingless-Type Mammary Tumor Virus Integration-Site Family Member 5B (WNT5B) with Type 2 Diabetes Am J Hum Genet 75(5): 832-843.

13. Woods CG, Stricker S, Seemann P, Stern R, Cox J, et al. (2006) Mutations in WNT7A Cause a Range of Limb Malformations, Including Fuhrmann Syndrome and Al-Awadi/Raas-Rothschild/Schinzel Phocomelia Syndrome. Am J Hum Genet 79(2): 402-408.

14. Adaimy L, Chouery E, Megarbane H, Mroueh S, Delague V, et al. (2007) Mutation in WNT10A Is Associated with an Autosomal Recessive Ectodermal Dysplasia: The Odonto-onycho-dermal Dysplasia. Am J Hum Genet 81(4): 821-828.

15. Bohring A, Stamm T, Spaich C, Haase C, Spree K, et al. (2009) WNT10A mutations are a frequent cause of a broad spectrum of ectodermal dysplasia with sex-biased manifestation pattern in heterozygotes. Am J Hum Genet 85(1): 97-105.

16. Kantaputra P, Sripathomsawat W (2011) WNT10A and isolated hypodontia. Am J Med Genet A 155a(5): 1119-1122.

17. Ugur SA, Tolun A (2008) Homozygous WNT10b mutation and complex inheritance in Split-Hand/Foot Malformation. Hum Mol Genet 17(17): 2644-2653.

18. Yu P, Yang W, Han D, Wang X, Guo S, et al. (2016) Mutations in WNT10B Are Identified in Individuals with Oligodontia. Am J Hum Genet 99(1): 195-201.

19. Ohkawara B, Cabrera-Serrano M, Nakata T, Milone M, Asai N, et al. (2014) LRP4 third β-propeller domain mutations cause novel congenital myasthenia by compromising agrin-mediated MuSK signaling in a position-specific manner. Hum Mol Genet 23(7): 1856-1868.

20. Li Y, Pawlik B, Elcioglu N, Aglan M, Kayserili H, et al. (2010) LRP4 Mutations Alter Wnt/β-Catenin Signaling and Cause Limb and Kidney Malformations in Cenani-Lenz Syndrome. Am J Hum Genet 86(5): 696-706.

21. Leupin O, Piters E, Halleux C, Hu S, Kramer I, et al. (2011) Bone Overgrowth-associated Mutations in the LRP4 Gene Impair Sclerostin Facilitator Function. J Biol Chem 286(22): 19489-19500.

22. Toomes C, Bottomley HM, Jackson RM, Towns KV, Scott S, et al. (2004) Mutations in LRP5 or FZD4 Underlie the Common Familial Exudative Vitreoretinopathy Locus on Chromosome 11q. Am J Hum Genet 74(4): 721-730.

23. Van Wesenbeeck L, Cleiren E, Gram J, Beals RK, Benichou O, et al. (2003) Six Novel Missense Mutations in the LDL Receptor-Related Protein 5 (LRP5) Gene in Different Conditions with an Increased Bone Density. Am J Hum Genet 72(3): 763-771

24. Van Hul E, Gram J, Bollerslev J, Van Wesenbeeck L, Mathysen D, et al. (2002) Osteopetrosis, Hypophosphatemia, and Phosphaturia in a Young Man: A Case Presentation and Differential Diagnosis. J Bone Miner Res 17(6): 1111-1117.

25. Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, et al. (2001) LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. Cell 107(4): 513-523.

26. Cnossen WR, te Morsche RH, Hoischen A, Gilissen C, Chrispijn M, (2014) Whole-exome sequencing reveals LRP5 mutations and canonical Wnt signaling associated with hepatic cystogenesis. Proc Natl Acad Sci USA 111(14): 5343-5348.

27. Little RD, Carulli JP, Del Mastro RG, Dupuis J, Osborne M, (2002) A Mutation in the LDL Receptor-Related Protein 5 Gene Results in the Autosomal Dominant High-Bone-Mass Trait. Am J Hum Genet 70(1): 11-19.

28. Nguyen TV, Livshits G, Center JR, Yakovenko K, Eisman JA (2003) Genetic Determination of Bone Mineral Density: Evidence for a Major Gene. J Clin Endocrinol Metab 88(8): 3614-3620.

29. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL (2012) Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet 44(5): 491-501.

30. Massink MP, Creton MA, Spanevello F, Fennis WM, Cune MS, et al. (2015) Loss-of-Function Mutations in the WNT Co-receptor LRP6 Cause Autosomal-Dominant Oligodontia. Am J Hum Genet 97(4): 621-626.

31. Mani A, Radhakrishnan J, Wang H, Mani A, Mani MA, et al. (2007) LRP6 mutation in a family with early coronary disease and metabolic risk factors. Science 315(5816): 1278-1282.

32. Shen GQ, Li L, Girelli D, Seidelmann SB, Shaoqi Rao, et al. (2007) An LRP8 Variant Is Associated with Familial and Premature Coronary Artery Disease and Myocardial Infarction. Am J Hum Genet 81(4): 780-791.

33. White JJ, Mazzeu JF, Coban-Akdemir Z, Bayram Y, Bahrambeigi V, et al. (2018) WNT Signaling Perturbations Underlie the Genetic Heterogeneity of Robinow Syndrome. Am J Hum Genet 102(1): 27-43.

34. MacDonald ML, Goldberg YP, Macfarlane J, Samuels ME, Trese MT, et al. (2005) Clin Genet 67(4): 363-366.

35. Robitaille J, MacDonald ML, Kaykas A, Sheldahl LC, Zeisler J, et al. (2002) Mutant frizzled-4 disrupts retinal angiogenesis in familial exudative vitreoretinopathy. Nat Genet 32(2): 326-330.

36. Frojmark AS, Schuster J, Sobol M, Entesarian M, Kilander MBC, et al. (2011) Mutations in Frizzled 6 Cause Isolated Autosomal-Recessive Nail Dysplasia. Am J Hum Genet 88(6): 852-860.

37. Wang YK, Samos CH, Peoples R, Perez-Jurado LA, et al. (1997) A novel human homologue of the Drosophila frizzled wnt receptor gene binds wingless protein and is in the Williams syndrome deletion at 7q11.23. Hum Mol Genet 6(3): 465-472.

38. Tan-Sindhunata MB, Mathijssen IB, Smit M, Baas F, de Vries JI, et al. (2015) Eur J Hum Genet 23(9): 1151-1157.

39. Chevessier F, Faraut B, Ravel-Chapuis A, Richard P, Gaudon K, et al. (2004) MUSK, a new target for mutations causing congenital myasthenic syndrome. Hum Mol Genet 13(24): 3229-3240.

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40. Ha E, Kim MJ, Choi BK, Rho JJ, Oh DJ, et al. (2006) Positive association of obesity with single nucleotide polymorphisms of syndecan 3 in the Korean population. J Clin Endocrinol Metab 91(12): 5095-5099.

41. Diaz-Horta O, Abad C, Sennaroglu L, Foster J, DeSmidt A, et al. (2016) ROR1 is essential for proper innervation of auditory hair cells and hearing in humans and mice. PNAS 113(21): 5993-5998.

42. Oldridge M, Fortuna AM, Maringa M, Propping P, Mansour S, et al. (2000) Robustness--it's not where you think it is. Nat Genet 24(3): 275-278.

43. van Bokhoven H, Celli J, Kayserili H, van Beusekom E, Balci S, et al. (2000) Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet 25(4): 423-426.

44. Afzal AR, Rajab A, Fenske CD, Oldridge M, Elanko N, et al. (2000) Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. Nat Genet 25(4): 419-422.

45. Pilia G, Hughes-Benzie RM, MacKenzie A, Baybayan P, Chen EY, et al. (1996) Mutations in GPC3, a glypican gene, cause the Simpson-Golabi-Behmel overgrowth syndrome. Nat Genet 12(3): 241-247.

46. White GR, Kelsey AM, Varley JM, Birch JM (2002) Somatic glypican 3 (GPC3) mutations in Wilms' tumour. Br J Cancer 86(12): 1920-1922.

47. Campos-Xavier AB, Martinet D, Bateman J, Belluoccio D, Rowley L, et al. (2009) Mutations in the Heparan-Sulfate Proteoglycan Glypican 6 (GPC6) Impair Endochondral Ossification and Cause Recessive Omodysplasia. Am J Hum Genet 84(6): 760-770.

48. Loughlin J, Dowling B, Mustafa Z, Southam L, Chapman K (2002) Refined linkage mapping of a hip osteoarthritis susceptibility locus on chromosome 2q. Rheumatology (Oxford) 41(8): 955-956.

49. Kiper POS, Saito H, Gori F, Unger S, Hesse E, et al. (2016) Cortical-Bone Fragility-Insights from sFRP4 Deficiency in Pyle's Disease. N Engl J Med 374(26): 2553-2562.

50. Kim SJ, Bieganski T, Sohn YB, Kozlowski K, Semenov M, et al. (2011) Identification of signal peptide domain SOST mutations in autosomal dominant craniodiaphyseal dysplasia. Hum Genet 129(5): 497-502.

51. Brunkow ME, Gardner JC, Van Ness J, Paeper BW, Kovacevich BR, et al. (2001) Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. Am J Hum Genet 68(3): 577-589.

52. Balemans W, Patel N, Ebeling M, Van Hul E, Wuyts W, et al. (2002) Identification of a 52 kb deletion downstream of the *SOST* gene in patients with van Buchem disease. J Med Genet 39(2): 91-97.

53. Issa YA, Kamal L, Rayyan AA, Dweik D, Pierce S, et al. (2016) Mutation of KREMEN1, a modulator of Wnt signaling, is responsible for ectodermal dysplasia including oligodontia in Palestinian families. Eur J Hum Genet 24(10): 1430-1435.

54. Dinckan N, Du R, Petty LE, Coban Akdemir Z, Jhangiani SN, et al. (2018) Whole-Exome Sequencing Identifies Novel Variants for Tooth Agenesis. J Dent Res 97(1): 49-59.

55. Parma P, Radi O, Vidal V, Chaboissier MC, Dellambra E, et al. (2006) R-spondin1 is essential in sex determination, skin differentiation and malignancy. Nat Genet 38(11): 1304-1309.

56. Tomaselli S, Megiorni F, De Bernardo C, Felici A, Marrocco G, et al. (2008) Syndromic true hermaphroditism due to an R-spondin1 (RSPO1) homozygous mutation. Hum Mutat 29(2): 220-226.

57. Szenker Ravi E, Altunoglu U, Leushacke M, Bosso Lefevre C, Khatoo M, et al. (2018) RSPO2 inhibition of RNF43 and ZNRF3 governs limb development independently of LGR4/5/6. Nature 557(7706): 564-569.

58. Blaydon DC, Ishii Y, O'Toole EA, Unsworth HC, Teh MT, et al. (2006) The gene encoding R-spondin 4 (RSPO4), a secreted protein implicated in Wnt signaling, is mutated in inherited anonychia. Nat Genet 38(11): 1245-1247.

59. Chen ZY, Battinelli EM, Fielder A, Bundey S, Sims K, et al. (1993) A mutation in the Norrie disease gene (NDP) associated with X-linked familial exudative vitreoretinopathy. Nat Genet 5(2): 180-183.

60. Schuback DE, Chen ZY, Craig IW, Breakefield XO, Sims KB (1995) Mutations in the Norrie disease gene. Hum Mutat 5(4): 285-292.

61. Styrkarsdottir U, Thorleifsson G, Sulem P, Gudbjartsson DF, Sigurdsson A, et al. (2013) Nonsense mutation in the LGR4 gene is associated with several human diseases and other traits. Nature 497(7450): 517-520.

62. Gala MK, Mizukami Y, Le LP, Moriichi K, Austin T, et al. (2014) Germline mutations in oncogene-induced senescence pathways are associated with multiple sessile serrated adenomas. Gastroenterology 146(2): 520-529.

63. White J, Mazzeu JF, Hoischen A, Jhangiani SN, Gambin T, et al. (2015) DVL1 Frameshift Mutations Clustering in the Penultimate Exon Cause Autosomal-Dominant Robinow Syndrome. Am J Hum Genet 96(4): 612-622.

64. White JJ, Mazzeu JF, Hoischen A, Bayram Y, Withers M, et al. (2016) DVL3 Alleles Resulting in a -1 Frameshift of the Last Exon Mediate Autosomal-Dominant Robinow Syndrome. Am J Hum Genet 98(3): 553-561.

65. Oates NA, van Vliet J, Duffy DL, Kroes HY, Martin NG, et al. (2006) Increased DNA Methylation at the AXIN1 Gene in a Monozygotic Twin from a Pair Discordant for a Caudal Duplication Anomaly. Am J Hum Genet 79(1): 155-162.

66. Taniguchi K, Roberts LR, Aderca IN, Dong X, Qian C, et al. (2002) Mutational spectrum of beta-catenin, AXIN1, and AXIN2 in hepatocellular carcinomas and hepatoblastomas. Oncogene 21(31): 4863-4871.

67. Fearnhead NS, Wilding JL, Winney B, Tonks S, Bartlett S, et al. (2004) Multiple rare variants in different genes account for multifactorial inherited susceptibility to colorectal adenomas. Proc Natl Acad Sci USA 101(45): 15992-15997.

68. Lammi L, Arte S, Somer M, Jarvinen H, Lahermo P, et al. (2004) Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. Am J Hum Genet 74(5): 1043-1050.

69. Morin PJ, Sparks AB, Korinek V, Barker N, Clevers H, et al. (1997) Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. Science 275(5307): 1787-1790.

70. Panagiotou ES, Sanjurjo Soriano C, Poulter JA, Lord EC, Dzulova D, et al. (2017) Defects in the Cell Signaling Mediator β-Catenin Cause the Retinal Vascular Condition FEVR. Am J Hum Genet 100(6): 960-968.

71. Koch A, Denkhaus D, Albrecht S, Leuschner I, von Schweinitz D, et al. (1999) Childhood hepatoblastomas frequently carry a mutated degradation targeting box of the beta-catenin gene. Cancer Res 59(2): 269-273.

72. Chan TA, Wang Z, Dang LH, Vogelstein B, Kinzler KW (2002) Targeted inactivation of CTNNB1 reveals unexpected effects of beta-catenin mutation. Proc Natl Acad Sci USA 99(12): 8265-8270.

73. Pugh TJ, Weeraratne SD, Archer TC, Pomeranz Krummel DA, et al. (2012) Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. Nature 488(7409): 106-110.

74. Tucci V, Kleefstra T, Hardy A, Heise I, Maggi S, et al. (2014) Dominant β-catenin mutations cause intellectual disability with recognizable syndromic features. J Clin Invest 124(4): 1468-1482.

75. Sagae S, Kobayashi K, Nishioka Y, Sugimura M, Ishioka S, et al. (1999) Mutational Analysis of β-Catenin Gene in Japanese Ovarian Carcinomas: Frequent Mutations in Endometrioid Carcinomas. Jpn J Cancer Res 90(5): 510-515.

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76. Asimaki A, Syrris P, Wichter T, Matthias P, Saffitz JE, et al. (2007) A Novel Dominant Mutation in Plakoglobin Causes Arrhythmogenic Right Ventricular Cardiomyopathy. J Hum Genet 81(5): 964-973.

77. Cabral RM, Liu L, Hogan C, Dopping-Hepenstal PJ, Winik BC, et al. (2010) Homozygous mutations in the 5' region of the JUP gene result in cutaneous disease but normal heart development in children. J Invest Dermatol 130(6): 1543-1550.

78. Groden J, Thliveris A, Samowitz W, Carlson M, Gelbert L, et al. (1991) Identification and characterization of the familial adenomatous polyposis coli gene. 66(3): 589-600.

79. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, et al. (1995) The molecular basis of Turcot's syndrome. N Engl J Med 332(13): 839-847.

80. Bapat B, Odze R, Mitri A, Berk T, Ward M, et al. (1993) Hum Mol Genet 2(11): 1957-1959.

81. Nishisho I, Nakamura Y, Miyoshi Y, Miki Y, Ando H, et al. (1991) Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science 253(5020): 665-669.

82. Scott RJ, Froggatt NJ, Trembath RC, Evans DG, Hodgson SV, et al. (1996) Familial infiltrative fibromatosis (desmoid tumours) (MIM135290) caused by a recurrent 3' APC gene mutation. Hum Mol Genet 5(12): 1921-1924.

83. Horii A, Nakatsuru S, Miyoshi Y, Ichii S, Nagase H, et al. (1992) The APC Gene, Responsible for Familial Adenomatous Polyposis, Is Mutated in Human Gastric Cancer[1]. Cancer Res 52(11): 3231-3233.

84. Su LK, Abdalla EK, Law CH, Kohlmann W, Rashid A, et al. (2001) Biallelic inactivation of the APC gene is associated with hepatocellular carcinoma in familial adenomatous polyposis coli. Cancer 92(2): 332-339.

85. Almuriekhi M, Shintani T, Fahiminiya S, Fujikawa A, Kuboyama K, et al. (2015) Loss-of-Function Mutation in APC2 Causes Sotos Syndrome Features. Cell Rep 10(9): 1585-1598.

86. Xu Y, Padiath QS, Shapiro RE, Jones CR, Wu SC, et al. (2005) Functional consequences of a CKIdelta mutation causing familial advanced sleep phase syndrome. Nature 434(7033): 640-644.

87. Takeda H, Lyle S, Lazar AJ, Zouboulis CC, Smyth I, et al. (2006) Human sebaceous tumors harbor inactivating mutations in LEF1. Nat Med 12(4): 395-397.

88. Boisson B, Wang YD, Bosompem A, Ma CS, Lim A, et al. (2013) A recurrent dominant negative E47 mutation causes agammaglobulinemia and BCR (-) B cells. J Clin Invest 123(11): 4781-4785.

89. Soliman AZ, Xing C, Radwan SH, Gong X, Mootha VV (2015) Correlation of Severity of Fuchs Endothelial Corneal Dystrophy With Triplet Repeat Expansion in TCF4. JAMA Ophthalmol 133(12): 1386-1391.

90. Amiel J, Rio M, de Pontual L, Redon R, Malan V, et al. (2007) Mutations in TCF4, encoding a class I basic helix-loop-helix transcription factor, are responsible for Pitt-Hopkins syndrome, a severe epileptic encephalopathy associated with autonomic dysfunction. Am J Hum Genet 80(5): 988-993.

91. Glazov EA, Zankl A, Donskoi M, Kenna TJ, Thomas GP, et al. (2011) Whole-exome re-sequencing in a family quartet identifies POP1 mutations as the cause of a novel skeletal dysplasia. PLoS Genet 7(3): e1002027.

92. Zhu X, Petrovski S, Xie P, Ruzzo EK, Lu YF, et al. (2015) Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios. Genet Med (10): 774-781.

93. Wang X, Reid Sutton V, Omar Peraza Llanes J, Yu Z, Rosetta R, et al. (2007) Mutations in X-linked PORCN, a putative regulator of Wnt signaling, cause focal dermal hypoplasia. Nat Genet 39(7): 836-838.

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