Supplementary Table 1. Mutations found in patients with genetic conditions and concurrent pilomatricomas[†]

Reference	Patient			Germline mutation	Somatic mutation
	Age (years)	Gender	Number of pilomatricomas		
Gardner syndrome					
Trufant et al., 2012 [3][††]	12	Male	Multiple	2 bp deletion (c.426_427delAT) in exon 4 of *APC* gene → frameshift (p.Ser142fs*146)	Lower nuclear beta-catenin protein in basaloid component than in sporadic pilomatricomas
	14	Female	Multiple		
Bendelsmith et al., 2018 [4]	11	Female	Multiple	Duplication (c.595dupG) in *APC* gene → frameshift (p.Ala199Glyfs*53)	NA
MYH-associated polyposis					
Baglioni et al., 2005 [31][††]	32	Male	Multiple	Homozygous 2 bp insertion (c.1186_1187insGG) in exon 13 of *MYH* gene → premature stop codon at position 438	No mutations in exon 3 of *CTNNB1* gene
	29	Female	Multiple		
Rubinstein-Taybi syndrome					
Rokunohe et al., 2016 [9]	12	female	Multiple	Duplication (c.5837dupC) in exon 31 of *CREBBP* gene → frameshift (p.Pro1947Thrfs*19)	c.122C>T (p.Thr41Ile) at phosphorylation site of beta-catenin protein
Papathemeli et al., 2015 [8]	49	Female	Multiple	Point mutation (c.6127C>T) in exon 31 of *CREBBP* gene → nonsense (p.Glu2043*)	NA
Turner syndrome					
Maeda et al., 2014 [21]	22	Female	Multiple	NA	Expression of beta-catenin protein in nuclei of basaloid cells
Handler et al., 2013 [20]	5	Female	Solitary	45,X	NA
	15	Female	Solitary	45,X/46,X,idic(X)	NA
	24	Female	Multiple	45,X	NA
	16	Female	Multiple	45,X	NA
	11	Female	Multiple	46,X,del(X)(p11.22)	NA
	9	Female	Multiple	45,X/46,X,idic(Y)(p11.3)/47,X,idic(Y)(p11.3),idic(Y)(p11.3)	NA
	10	Female	Solitary	45,X/46,X,r(X)	NA
	4	Female	Solitary	45,X/46,X,psu dic(Y)(p11.3)	NA
Bengtzen et al., 2009 [19]	13	Female	Multiple	45,X/46,XY	NA
Noguchi et al., 1999 [17]	23	Female	Solitary	45,X	NA
	19	Female	Multiple	45,X/46,X,i(Xq)	NA

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	Age (years)	Gender	Number of pilomatricomas		
Sotos syndrome					
Gilaberte et al., 2008 [28]	9	Male	Multiple	Deletion (A6442delAGCGACCA, Lys2151fs*) in exon 22 of *NSD1* gene	Same deletion of *NSD1* gene No mutations of *CTNNB1* gene
Constitutional mismatch repair deficiency					
Chmara et al., 2013 [27]	11	Male	Multiple	Homozygous mutation, c.1164delT in exon 11 of *PMS2* gene → premature stop codon (p.His388Glnfs*9)	- No microsatellite instability in pilomatricoma tissues - Loss of nuclear PMS2 protein expression in neoplastic and non-neoplastic cells in pilomatricoma tissues - c.94G>T (p.Asp32Tyr), c.122C>T (p.Thr41Ile), c.121A>G (p.Thr41Ala), c.97T>C (p.Ser33Pro) in exon 3 of *CTNNB1* gene
	4	Female	Multiple	Maternal deletion of exons 7–8 c.(?_706)_(9031_?)del and paternal a deletion of exons 9–15 c.(?_904)_(*+_?)del of *PMS2* gene	- No microsatellite instability in pilomatricoma tissues - Loss of nuclear PMS2 protein expression in neoplastic and non-neoplastic cells in pilomatricoma tissues - c.122C>T (p.Thr41Ile) in exon 3 of *CTNNB1* gene
	15	Male	Multiple	Heterozygous splice site mutation, c.705+2T>C in *PMS2* intron 6 and heterozygosity for 3 exonic polymorphic variants, including c.780C>G, c.1408C>T, and c.1621A>G	- c.122C>T (p.Thr41Ile), c.121A>G (p.Thr41Ala), c.97T>C (p.Ser33Pro) in exon 3 of *CTNNB1*gene
Myotonic dystrophy					
Rübben et al., 2020 [11]	39	Male	Multiple pilomatricomas and one pilomatrical carcinoma	> 400 CTG-repeat expansion in *DMPK* gene Heterozygous mutation c.8494C>T (p.Arg2832Cys) in exon 3 of *ATM* gene	p.Ser33Cys, p.Ser33Phe, p.Gly34Val, p.Thr41Ile and p.Gly34dup of *CTNNB1* gene No abnormal microsatellites and no mutations of mismatch repair genes (*MLH1, MSH2, MSH6,* and *PMS2*) Heterozygous mutation c.8494C>T (p.Arg2832Cys) in *ATM* gene
Gain of chromosome 9 materials					
Matsuura et al., 2002 [33]	4	Female	Multiple	47,XX, +mar[22]/46,XX[8].ish i(9)(p10)(wcp9+) i(9) in 26.7% of cultured lymphocyte	NA

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Reference	Patient			Germline mutation	Somatic mutation
	Age (years)	Gender	Number of pilomatricomas		
Blaya et al., 2009 [32]	15	Male	Multiple	46 XY (42.4%)/47 XY + del9 (pter-q32) (57.6%)[†††] +del(9) in 57.6% of cultured lymphocyte	NA
El Khattabi et al., 2015 [34]	18	Female	Multiple	47,XX,+psu idic(9)(pter→q21::q21→pter) idic(9) in 90% of cultured lymphocytes, 30% in cultured skin fibroblasts and 30% in urine sediment	NA
	7.5	Female	Multiple	47,XY,+psu idic(9)(pter→q12 or 13::q13 or 12→pter) idic(9) in 90% of cultured lymphocytes	NA
	18	Female	Multiple	47,XY,+psu idic(9)(pter→q12 or 13::q13 or 12→pter) idic(9) in 75% of cultured lymphocytes, 0% in cultured skin fibroblasts and 40% in buccal smear	NA
Our patient	4	Female	? Multiple	47,XX,+psu idic(9)(q12).arr [GRCh37] 9p24.3p12(46,587_42,374,011)x4 dn 100% of idic(9) in of cultured lymphocytes (20/20 cells), 8.3% of idic(9) in cultured skin fibroblasts (3/36 cells)	0% of idic(9) in pilomatricoma (0/27 cells) No beta-catenin and bcl2 protein expression in basaloid component

[†] Only patients with information regarding mutations are included in the table. Association between pilomatricoma and some genetic conditions have been suggested; wherein, tumorigenesis has been linked between genes responsible for these genetic conditions in addition to beta-catenin regulation in Wnt signaling pathways. In Wnt signaling pathways, adenomatous polyposis coli, axin1, casein kinase 1 alpha, and glycogen synthase kinase 3 beta proteins are components of beta-catenin destruction complex. The complex binds to beta-catenin, and sequentially phosphorylate beta-catenin, targeting it for ubiquitin-dependent degradation by the proteasome [37]. Mutations of *APC* genes, which are responsible for Gardner syndrome, result in truncated APC proteins, and ultimately lead to an accumulation of beta-catenin protein [3]. Linking between genes responsible for other genetic conditions and pilomatricoma have been hypothesized with some supporting evidences. For example, mutations of *CREBBP* gene on chromosome 16p13.3 are responsible for Rubinstein Taybi syndrome. *CREBBP* gene plays a role in the maintenance of genomic integrity in stem cells, and initiation of a differentiation by controlling the interaction of the nuclear receptor family with the Wnt signaling cascade [a]. In tuberous sclerosis complex, mutations of *TSC1* and *TSC2* genes on chromosome 9q34 and 16p13.3, respectively, are responsible for the disease. TSC1/TSC2 protein complex is associated with glycogen synthase kinase 3 beta and axin1 proteins, which in turn, promotes beta-catenin degradation. Missense mutation of *TSC* gene caused its failure to inhibit beta-catenin [26, b]. In Turner syndrome, low levels of glypican-3 protein, encoded by *GPC3* gene on chromosome Xq26.2, results in increases of beta-catenin [20]. In constitutive mismatch repair deficiency, *CTNNB1* gene is a target for mutations when mismatched repair is impaired due to biallelic *PMS2* mutations [27].

References

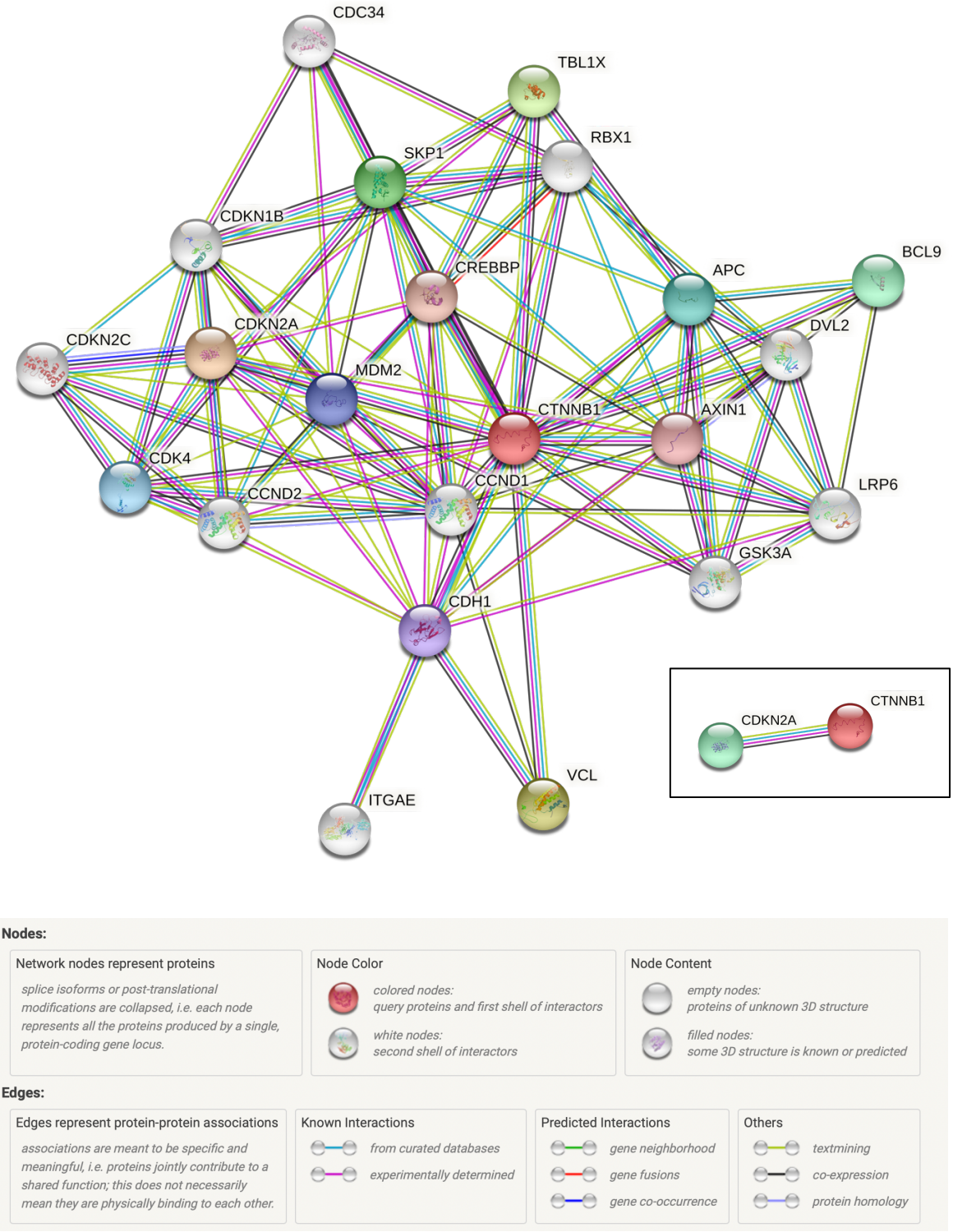
a. M. Ono, K.K.Y. Lai, K. Wu, et al., "Nuclear receptor/Wnt beta-catenin interactions are regulated via differential CBP/p300 coactivator usage." *PLOS ONE*. vol. 13, no. 7, pp. e0200714, 2018.

b. B.C. Mak, H.L. Kenerson, L.D. Aicher, et al., "Aberrant beta-catenin signaling in tuberous sclerosis." *The American Journal of Pathology*. vol. 167, no. 1, pp. 107–116, 2005.

[††] Study of siblings with the same genetic conditions.

[††] Cytogenetic nomenclature remains the same as in the publication.

Supplementary Figure 1. Gene network shows interactions between *CTNNB1* gene and other genes, including *CDKN2A* gene on chromosome 9 (https://string-db.org/).



Nodes:

Network nodes represent proteins

splice isoforms or post-translational modifications are collapsed, i.e. each node represents all the proteins produced by a single, protein-coding gene locus.

Node Color

colored nodes: query proteins and first shell of interactors

white nodes: second shell of interactors

Node Content

empty nodes: proteins of unknown 3D structure

filled nodes: some 3D structure is known or predicted

Edges:

Edges represent protein-protein associations

associations are meant to be specific and meaningful, i.e. proteins jointly contribute to a shared function; this does not necessarily mean they are physically binding to each other.

Known Interactions

from curated databases

experimentally determined

Predicted Interactions

gene neighborhood

gene fusions

gene co-occurrence

Others

textmining

co-expression

protein homology