Cell, Volume *137*

The Vertebrate Primary Cilium in Development, Homeostasis, and Disease

Jantje M. Gerdes, Erica E. Davis, and Nicholas Katsanis

Table 1. Phenotypic Overlap and Genes Associated with Ciliopathies

	Ciliopathy	Leber Congenital Amaurosis	Nephronophthisis	Senior-Loken Syndrome	Joubert Syndrome	Bardet-Biedl Syndrome	Meckel-Gruber Syndrome	Reference
Phenotype	cerebellar hypoplasia		X		**X**	X		
	encephalocele						**X**	
	hepatic disease		X	X	X	X	**X**	
	kidney disease		**X**	**X**	**X**	**X**	**X**	
	mental retardation	X	X		**X**	**X**		
	obesity				X	**X**		
	polydactyly				X	**X**	**X**	
	retinopathy	**X**	X	**X**	**X**	**X**		
	situs inversus			X	X	X	X	
Gene	*AIPL1*	X						Sohocki et al., 2000
	CRB1	X						Lotery et al., 2001, den Hollander et al., 2001
	CRX	X						Freund et al., 1998
	GUCY2D	X						Perrault et al., 1996
	IMPDH1	X						Bowne et al., 2006
	RDH12	X						Perrault et al., 2004
	RPE65	X						Marlhens et al., 1997
	RPGRIP1	X						Dryja et al., 2001
	LCA5	X						den Hollander et al., 2007
	CEP290	X	X	X	X	X	X	den Hollander et al., 2006, Sayer et al., 2006, Valente et al., 2006, Leitch et al., 2008, Baala et al., 2007
	NPHP1		X	X	X			Hildebrandt et al., 1997, Hildebrandt et al., 2007, Parisi et al., 2004
	INVS		X	X				Otto et al., 2003, O'Toole et al., 2006
	NPHP3		X	X			X	Olbrich et al., 2003, Bergmann et al., 2008
	NPHP4		X	X				Mollet et al., 2002, Otto et al., 2002
	NPHP5		X	X				Otto et al., 2005
	GLIS2		X					Attanasio et al., 2007
	NEK8		X					Otto et al., 2008
	AHI1				X			Ferland et al., 2004, Dixon-Salazar et al., 2004
	TMEM67				X	X	X	Baala et al., 2007, Leitch et al., 2008, Smith et al., 2006
	RPGRIP1L		X		X		X	Wolf et al., 2007, Arts et al., 2007, Delous et al., 2007
	ARL13B				X			Cantagrel et al., 2008
	BBS1					X		Mkytyn et al., 2002
	BBS2					X	X	Nishimura et al., 2001, Karmous-Benailly et al., 2005
	BBS3					X		Fan et al., 2004, Chiang et al., 2004
	BBS4					X	X	Myktyn et al., 2001, Karmous-Benailly et al., 2005
	BBS5					X		Li et al., 2004
	BBS6					X	X	Katsanis et al., 2000, Karmous-Benailly et al., 2005
	BBS7					X		Badano et al., 2003
	BBS8					X		Ansley et al., 2003
	BBS9					X		Nishimura et al., 2005
	BBS10					X		Stoetzel et al., 2006
	BBS11					X		Chiang et al., 2006
	BBS12					X		Stoetzel et al., 2007
	MGC1203					X		Badano et al., 2006
	MKS1					X	X	Kyttala et al., 2006, Leitch et al., 2008
	CC2D2A				X		X	Tallila et al., 2008, Gorden et al., 2008

Bold type indicates primary phenotypic characteristics. Phenotypic severity increases left to right.

Supplemental References

Ansley, S. J., Badano, J. L., Blacque, O. E., Hill, J., Hoskins, B. E., Leitch, C. C., Kim, J. C., Ross, A. J., Eichers, E. R., Teslovich, T. M.*, et al.* (2003). Basal body dysfunction is a likely cause of pleiotropic Bardet-Biedl syndrome. Nature *425*, 628-633.

Arts, H. H., Doherty, D., van Beersum, S. E., Parisi, M. A., Letteboer, S. J., Gorden, N. T., Peters, T. A., Marker, T., Voesenek, K., Kartono, A.*, et al.* (2007). Mutations in the gene encoding the basal body protein RPGRIP1L, a nephrocystin-4 interactor, cause Joubert syndrome. Nat Genet *39*, 882-888.

Attanasio, M., Uhlenhaut, N. H., Sousa, V. H., O'Toole, J. F., Otto, E., Anlag, K., Klugmann, C., Treier, A. C., Helou, J., Sayer, J. A.*, et al.* (2007). Loss of GLIS2 causes nephronophthisis in humans and mice by increased apoptosis and fibrosis. Nat Genet *39*, 1018-1024.

Baala, L., Audollent, S., Martinovic, J., Ozilou, C., Babron, M. C., Sivanandamoorthy, S., Saunier, S., Salomon, R., Gonzales, M., Rattenberry, E.*, et al.* (2007a). Pleiotropic effects of CEP290 (NPHP6) mutations extend to Meckel syndrome. Am J Hum Genet *81*, 170-179.

Baala, L., Romano, S., Khaddour, R., Saunier, S., Smith, U. M., Audollent, S., Ozilou, C., Faivre, L., Laurent, N., Foliguet, B.*, et al.* (2007b). The Meckel-Gruber syndrome gene, MKS3, is mutated in Joubert syndrome. Am J Hum Genet *80*, 186-194.

Badano, J. L., Ansley, S. J., Leitch, C. C., Lewis, R. A., Lupski, J. R., and Katsanis, N. (2003). Identification of a novel Bardet-Biedl syndrome protein, BBS7, that shares structural features with BBS1 and BBS2. Am J Hum Genet *72*, 650-658.

Badano, J. L., Leitch, C. C., Ansley, S. J., May-Simera, H., Lawson, S., Lewis, R. A., Beales, P. L., Dietz, H. C., Fisher, S., and Katsanis, N. (2006). Dissection of epistasis in oligogenic Bardet-Biedl syndrome. Nature *439*, 326-330.

Bergmann, C., Fliegauf, M., Bruchle, N. O., Frank, V., Olbrich, H., Kirschner, J., Schermer, B., Schmedding, I., Kispert, A., Kranzlin, B.*, et al.* (2008). Loss of nephrocystin-3 function can cause embryonic lethality, Meckel-Gruber-like syndrome, situs inversus, and renal-hepatic-pancreatic dysplasia. Am J Hum Genet *82*, 959-970.

Bowne, S. J., Sullivan, L. S., Mortimer, S. E., Hedstrom, L., Zhu, J., Spellicy, C. J., Gire, A. I., Hughbanks-Wheaton, D., Birch, D. G., Lewis, R. A.*, et al.* (2006). Spectrum and frequency of mutations in IMPDH1 associated with autosomal dominant retinitis pigmentosa and leber congenital amaurosis. Invest Ophthalmol Vis Sci *47*, 34-42.

Cantagrel, V., Silhavy, J. L., Bielas, S. L., Swistun, D., Marsh, S. E., Bertrand, J. Y., Audollent, S., Attie-Bitach, T., Holden, K. R., Dobyns, W. B.*, et al.* (2008). Mutations in the cilia gene ARL13B lead to the classical form of Joubert syndrome. Am J Hum Genet *83*, 170-179.

Chiang, A. P., Beck, J. S., Yen, H. J., Tayeh, M. K., Scheetz, T. E., Swiderski, R. E., Nishimura, D. Y., Braun, T. A., Kim, K. Y., Huang, J.*, et al.* (2006). Homozygosity mapping with SNP arrays identifies TRIM32, an E3 ubiquitin

ligase, as a Bardet-Biedl syndrome gene (BBS11). Proc Natl Acad Sci U S A *103*, 6287-6292.
Chiang, A. P., Nishimura, D., Searby, C., Elbedour, K., Carmi, R., Ferguson, A. L., Secrist, J., Braun, T., Casavant, T., Stone, E. M., and Sheffield, V. C. (2004). Comparative genomic analysis identifies an ADP-ribosylation factor-like gene as the cause of Bardet-Biedl syndrome (BBS3). Am J Hum Genet *75*, 475-484.
Delous, M., Baala, L., Salomon, R., Laclef, C., Vierkotten, J., Tory, K., Golzio, C., Lacoste, T., Besse, L., Ozilou, C*., et al.* (2007). The ciliary gene RPGRIP1L is mutated in cerebello-oculo-renal syndrome (Joubert syndrome type B) and Meckel syndrome. Nat Genet *39*, 875-881.
den Hollander, A. I., Heckenlively, J. R., van den Born, L. I., de Kok, Y. J., van der Velde-Visser, S. D., Kellner, U., Jurklies, B., van Schooneveld, M. J., Blankenagel, A., Rohrschneider, K*., et al.* (2001). Leber congenital amaurosis and retinitis pigmentosa with Coats-like exudative vasculopathy are associated with mutations in the crumbs homologue 1 (CRB1) gene. Am J Hum Genet *69*, 198-203.
den Hollander, A. I., Koenekoop, R. K., Mohamed, M. D., Arts, H. H., Boldt, K., Towns, K. V., Sedmak, T., Beer, M., Nagel-Wolfrum, K., McKibbin, M*., et al.* (2007). Mutations in LCA5, encoding the ciliary protein lebercilin, cause Leber congenital amaurosis. Nat Genet *39*, 889-895.
den Hollander, A. I., Koenekoop, R. K., Yzer, S., Lopez, I., Arends, M. L., Voesenek, K. E., Zonneveld, M. N., Strom, T. M., Meitinger, T., Brunner, H. G*., et al.* (2006). Mutations in the CEP290 (NPHP6) gene are a frequent cause of Leber congenital amaurosis. Am J Hum Genet *79*, 556-561.
Dixon-Salazar, T., Silhavy, J. L., Marsh, S. E., Louie, C. M., Scott, L. C., Gururaj, A., Al-Gazali, L., Al-Tawari, A. A., Kayserili, H., Sztriha, L., and Gleeson, J. G. (2004). Mutations in the AHI1 gene, encoding jouberin, cause Joubert syndrome with cortical polymicrogyria. Am J Hum Genet *75*, 979-987.
Dryja, T. P., Adams, S. M., Grimsby, J. L., McGee, T. L., Hong, D. H., Li, T., Andreasson, S., and Berson, E. L. (2001). Null RPGRIP1 alleles in patients with Leber congenital amaurosis. Am J Hum Genet *68*, 1295-1298.
Fan, Y., Esmail, M. A., Ansley, S. J., Blacque, O. E., Boroevich, K., Ross, A. J., Moore, S. J., Badano, J. L., May-Simera, H., Compton, D. S*., et al.* (2004). Mutations in a member of the Ras superfamily of small GTP-binding proteins causes Bardet-Biedl syndrome. Nat Genet *36*, 989-993.
Ferland, R. J., Eyaid, W., Collura, R. V., Tully, L. D., Hill, R. S., Al-Nouri, D., Al-Rumayyan, A., Topcu, M., Gascon, G., Bodell, A*., et al.* (2004). Abnormal cerebellar development and axonal decussation due to mutations in AHI1 in Joubert syndrome. Nat Genet *36*, 1008-1013.
Freund, C. L., Wang, Q. L., Chen, S., Muskat, B. L., Wiles, C. D., Sheffield, V. C., Jacobson, S. G., McInnes, R. R., Zack, D. J., and Stone, E. M. (1998). De novo mutations in the CRX homeobox gene associated with Leber congenital amaurosis. Nat Genet *18*, 311-312.
Gorden, N. T., Arts, H. H., Parisi, M. A., Coene, K. L., Letteboer, S. J., van Beersum, S. E., Mans, D. A., Hikida, A., Eckert, M., Knutzen, D*., et al.* (2008). CC2D2A is mutated in Joubert syndrome and interacts with the

ciliopathyassociated basal body protein CEP290. Am J Hum Genet *83*, 559-571.
Hildebrandt, F., Otto, E., Rensing, C., Nothwang, H. G., Vollmer, M., Adolphs, J., Hanusch, H., and Brandis, M. (1997). A novel gene encoding an SH3 domain protein is mutated in nephronophthisis type 1. Nat Genet *17*, 149-153.
Hildebrandt, F., and Zhou, W. (2007). Nephronophthisis-associated ciliopathies. J Am Soc Nephrol *18*, 1855-1871.
Karmous-Benailly, H., Martinovic, J., Gubler, M. C., Sirot, Y., Clech, L., Ozilou, C., Auge, J., Brahimi, N., Etchevers, H., Detrait, E.*, et al.* (2005). Antenatal presentation of Bardet-Biedl syndrome may mimic Meckel syndrome. Am J Hum Genet *76*, 493-504.
Katsanis, N., Beales, P. L., Woods, M. O., Lewis, R. A., Green, J. S., Parfrey, P. S., Ansley, S. J., Davidson, W. S., and Lupski, J. R. (2000). Mutations in MKKS cause obesity, retinal dystrophy and renal malformations associated with Bardet-Biedl syndrome. Nat Genet *26*, 67-70.
Kyttala, M., Tallila, J., Salonen, R., Kopra, O., Kohlschmidt, N., Paavola-Sakki, P., Peltonen, L., and Kestila, M. (2006). MKS1, encoding a component of the flagellar apparatus basal body proteome, is mutated in Meckel syndrome. Nat Genet *38*, 155-157.
Leitch, C. C., Zaghloul, N. A., Davis, E. E., Stoetzel, C., Diaz-Font, A., Rix, S., Alfadhel, M., Lewis, R. A., Eyaid, W., Banin, E.*, et al.* (2008). Hypomorphic mutations in syndromic encephalocele genes are associated with Bardet- Biedl syndrome. Nat Genet *40*, 443-448.
Li, J. B., Gerdes, J. M., Haycraft, C. J., Fan, Y., Teslovich, T. M., May-Simera, H., Li, H., Blacque, O. E., Li, L., Leitch, C. C.*, et al.* (2004). Comparative genomics identifies a flagellar and basal body proteome that includes the BBS5 human disease gene. Cell *117*, 541-552.
Lotery, A. J., Jacobson, S. G., Fishman, G. A., Weleber, R. G., Fulton, A. B., Namperumalsamy, P., Heon, E., Levin, A. V., Grover, S., Rosenow, J. R.*, et al.* (2001). Mutations in the CRB1 gene cause Leber congenital amaurosis. Arch Ophthalmol *119*, 415-420.
Marlhens, F., Bareil, C., Griffoin, J. M., Zrenner, E., Amalric, P., Eliaou, C., Liu, S. Y., Harris, E., Redmond, T. M., Arnaud, B.*, et al.* (1997). Mutations in RPE65 cause Leber's congenital amaurosis. Nat Genet *17*, 139-141.
Mollet, G., Salomon, R., Gribouval, O., Silbermann, F., Bacq, D., Landthaler, G., Milford, D., Nayir, A., Rizzoni, G., Antignac, C., and Saunier, S. (2002). The gene mutated in juvenile nephronophthisis type 4 encodes a novel protein that interacts with nephrocystin. Nat Genet *32*, 300-305.
Mykytyn, K., Braun, T., Carmi, R., Haider, N. B., Searby, C. C., Shastri, M., Beck, G., Wright, A. F., Iannaccone, A., Elbedour, K.*, et al.* (2001). Identification of the gene that, when mutated, causes the human obesity syndrome BBS4. Nat Genet *28*, 188-191.
Mykytyn, K., Nishimura, D. Y., Searby, C. C., Shastri, M., Yen, H. J., Beck, J. S., Braun, T., Streb, L. M., Cornier, A. S., Cox, G. F.*, et al.* (2002). Identification of the gene (BBS1) most commonly involved in Bardet-Biedl syndrome, a complex human obesity syndrome. Nat Genet *31*, 435-438.

Nishimura, D. Y., Searby, C. C., Carmi, R., Elbedour, K., Van Maldergem, L., Fulton, A. B., Lam, B. L., Powell, B. R., Swiderski, R. E., Bugge, K. E.*, et al.* (2001). Positional cloning of a novel gene on chromosome 16q causing Bardet-Biedl syndrome (BBS2). Hum Mol Genet *10*, 865-874.
Nishimura, D. Y., Swiderski, R. E., Searby, C. C., Berg, E. M., Ferguson, A. L., Hennekam, R., Merin, S., Weleber, R. G., Biesecker, L. G., Stone, E. M., and Sheffield, V. C. (2005). Comparative genomics and gene expression analysis identifies BBS9, a new Bardet-Biedl syndrome gene. Am J Hum Genet *77*, 1021-1033.
O'Toole, J. F., Otto, E. A., Frishberg, Y., and Hildebrandt, F. (2006). Retinitis pigmentosa and renal failure in a patient with mutations in INVS. Nephrol Dial Transplant *21*, 1989-1991.
Olbrich, H., Fliegauf, M., Hoefele, J., Kispert, A., Otto, E., Volz, A., Wolf, M. T., Sasmaz, G., Trauer, U., Reinhardt, R.*, et al.* (2003). Mutations in a novel gene, NPHP3, cause adolescent nephronophthisis, tapeto-retinal degeneration and hepatic fibrosis. Nat Genet *34*, 455-459.
Otto, E., Hoefele, J., Ruf, R., Mueller, A. M., Hiller, K. S., Wolf, M. T., Schuermann, M. J., Becker, A., Birkenhager, R., Sudbrak, R.*, et al.* (2002). A gene mutated in nephronophthisis and retinitis pigmentosa encodes a novel protein, nephroretinin, conserved in evolution. Am J Hum Genet *71*, 1161-1167.
Otto, E. A., Loeys, B., Khanna, H., Hellemans, J., Sudbrak, R., Fan, S., Muerb, U., O'Toole, J. F., Helou, J., Attanasio, M.*, et al.* (2005). Nephrocystin-5, a ciliary IQ domain protein, is mutated in Senior-Loken syndrome and interacts with RPGR and calmodulin. Nat Genet *37*, 282-288.
Otto, E. A., Schermer, B., Obara, T., O'Toole, J. F., Hiller, K. S., Mueller, A. M., Ruf, R. G., Hoefele, J., Beekmann, F., Landau, D.*, et al.* (2003). Mutations in INVS encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. Nat Genet *34*, 413-420.
Otto, E. A., Trapp, M. L., Schultheiss, U. T., Helou, J., Quarmby, L. M., and Hildebrandt, F. (2008). NEK8 mutations affect ciliary and centrosomal localization and may cause nephronophthisis. J Am Soc Nephrol *19*, 587-592.
Parisi, M. A., Bennett, C. L., Eckert, M. L., Dobyns, W. B., Gleeson, J. G., Shaw, D. W., McDonald, R., Eddy, A., Chance, P. F., and Glass, I. A. (2004). The NPHP1 gene deletion associated with juvenile nephronophthisis is present in a subset of individuals with Joubert syndrome. Am J Hum Genet *75*, 82-91.
Perrault, I., Hanein, S., Gerber, S., Barbet, F., Ducroq, D., Dollfus, H., Hamel, C., Dufier, J. L., Munnich, A., Kaplan, J., and Rozet, J. M. (2004). Retinal dehydrogenase 12 (RDH12) mutations in leber congenital amaurosis. Am J Hum Genet *75*, 639-646.
Perrault, I., Rozet, J. M., Calvas, P., Gerber, S., Camuzat, A., Dollfus, H., Chatelin, S., Souied, E., Ghazi, I., Leowski, C.*, et al.* (1996). Retinal-specific guanylate cyclase gene mutations in Leber's congenital amaurosis. Nat Genet *14*, 461-464.
Sayer, J. A., Otto, E. A., O'Toole, J. F., Nurnberg, G., Kennedy, M. A., Becker, C., Hennies, H. C., Helou, J., Attanasio, M., Fausett, B. V.*, et al.* (2006). The

centrosomal protein nephrocystin-6 is mutated in Joubert syndrome and activates transcription factor ATF4. Nat Genet *38*, 674-681.
Smith, U. M., Consugar, M., Tee, L. J., McKee, B. M., Maina, E. N., Whelan, S., Morgan, N. V., Goranson, E., Gissen, P., Lilliquist, S.*, et al.* (2006). The transmembrane protein meckelin (MKS3) is mutated in Meckel-Gruber syndrome and the wpk rat. Nat Genet *38*, 191-196.
Sohocki, M. M., Bowne, S. J., Sullivan, L. S., Blackshaw, S., Cepko, C. L., Payne, A. M., Bhattacharya, S. S., Khaliq, S., Qasim Mehdi, S., Birch, D. G.*, et al.* (2000). Mutations in a new photoreceptor-pineal gene on 17p cause Leber congenital amaurosis. Nat Genet *24*, 79-83.
Stoetzel, C., Laurier, V., Davis, E. E., Muller, J., Rix, S., Badano, J. L., Leitch, C. C., Salem, N., Chouery, E., Corbani, S.*, et al.* (2006). BBS10 encodes a vertebrate-specific chaperonin-like protein and is a major BBS locus. Nat Genet *38*, 521-524.
Stoetzel, C., Muller, J., Laurier, V., Davis, E. E., Zaghloul, N. A., Vicaire, S., Jacquelin, C., Plewniak, F., Leitch, C. C., Sarda, P.*, et al.* (2007). Identification of a novel BBS gene (BBS12) highlights the major role of a vertebrate-specific branch of chaperonin-related proteins in Bardet-Biedl syndrome. Am J Hum Genet *80*, 1-11.
Tallila, J., Jakkula, E., Peltonen, L., Salonen, R., and Kestila, M. (2008). Identification of CC2D2A as a Meckel syndrome gene adds an important piece to the ciliopathy puzzle. Am J Hum Genet *82*, 1361-1367.
Valente, E. M., Silhavy, J. L., Brancati, F., Barrano, G., Krishnaswami, S. R., Castori, M., Lancaster, M. A., Boltshauser, E., Boccone, L., Al-Gazali, L.*, et al.* (2006). Mutations in CEP290, which encodes a centrosomal protein, cause pleiotropic forms of Joubert syndrome. Nat Genet *38*, 623-625.
Wolf, M. T., Saunier, S., O'Toole, J. F., Wanner, N., Groshong, T., Attanasio, M., Salomon, R., Stallmach, T., Sayer, J. A., Waldherr, R.*, et al.* (2007). Mutational analysis of the RPGRIP1L gene in patients with Joubert syndrome and nephronophthisis. Kidney Int *72*, 1520-1526.