

Table 1. Phenotypic overlap and genes contributing to total mutational load in six ciliopathies

Gene	► INCREASING PHENOTYPIC SEVERITY ►						Reference
	RP MR	KD RP, MR, CH, HD	KD, RP SI, HD	RP, KD, MR, CH P, SI, O, HD	RP, KD, MR, P, O CH, SI, HD	KD, P, HD, EN SI	
Gene	LCA	NPHP	SLS	JBTS	BBS	MKS	Reference
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

Ciliopathies- LCA: Leber congenital amaurosis, NPHP: Nephronophthisis, SLS: Senior-Loken Syndrome, JBTS: Joubert Syndrome, BBS: Bardet-Biedl Syndrome, MKS: Meckel-Gruber Syndrome

Phenotypic features- RP: Retinopathy, KD: Kidney disease, MR: Mental retardation, P: Polydactyly, O: Obesity, CH: Cerebellar hypoplasia, SI: Situs inversus, HD: Hepatic disease, EN: Encephalocele. Bold type indicates primary characteristics.

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., Voeselek, 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., Voeselek, 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 joubertin, 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 ciliopathy-associated 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., Brahim, 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., Zaghoul, 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.