Identification of 28 novel mutations in the Bardet-Biedl syndrome genes: the burden of private mutations in an extensively heterogeneous disease

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Identification of 28 novel mutations in the Bardet-Biedl syndrome genes: the burden of private mutations in an extensively heterogeneous disease

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Bardet-Biedl syndrome (BBS), an emblematic disease in the rapidly evolving field of ciliopathies, is characterized by pleiotropic clinical features and extensive genetic heterogeneity. To date, 14 BBS genes have been identified, 3 of which have been found mutated only in a single BBS family each (BBS11/TRIM32, BBS13/MKS1 and BBS14/MKS4/NPHP6). Previous reports of systematic mutation detection in large cohorts of BBS families (n > 90) have dealt only with a single gene, or at most small subsets of the known BBS genes. Here we report extensive analysis of a cohort of 174 BBS families for 12/14 genes, leading to the identification of 28 novel mutations. Two pathogenic mutations in a single gene have been found in 117 families, and a single heterozygous mutation in 17 families (of which 8 involve the BBS1 recurrent mutation, M390R). We confirm that BBS1 and BBS10 are the most frequently mutated genes, followed by BBS12. No mutations have been found in BBS11/TRIM32, the identification of which as a BBS gene only relies on a single missense mutation in a single consanguineous family. While a third variant allele has been observed in a few families, they are in most cases missenses of uncertain pathogenicity, contrasting with the type of mutations observed as two alleles in a single gene. We discuss the various strategies for diagnostic mutation detection, including homozygosity mapping and targeted arrays for the detection of previously reported mutations.

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