Candidate Gene Criteria for Clinical Reporting (V7-6-2016)

CLINICAL REPORT CLASSIFICATION	CATEGORY	CODE	CRITERION	EXCEPTIONS/ CAVEATS/ NOTES
Candidate	At least VLP according to Ambry Variant Classification (LaDuca, 2014), AND:			For inherited compound heterozygous alterations, both must be at least VLP
	A 1 needed*	C-A1	Gene located within the well-defined critical gene region of an established microdeletion/duplication syndrome with highly consistent features supportive of proposed gene-disease relationship	AD, XL only
		C-A2	Proposed candidate gene-disease relationship categorized as at least "limited" (Clinical Validity Classification) and patient's phenotype is highly consistent with reported patients	Ambry's Clinical Validity Classification Scheme (data in preparation) is inspired by the ClinGen Gene Curation classification (in preparation)
	B 2 needed*	C-B1	Protein co-localizes or physically interacts with the products of genes implicated in the proposed gene-disease relationship	No point if conflicting evidence; Predicted damaging alterations in expression-specific tissues have a high predictive predictability (Zaidi, 2013)
		C-B2	*in vivo* model organism with consistent genotype produces phenotype strongly supportive of the proposed gene-disease relationship	No point if conflicting evidence; Must consider specificity (*e.g.* short stature in mice not specific; observed in ~30% of knock-outs) (Reed, 2008)
		C-B3	Expression profile is strongly supportive of the proposed gene-disease relationship (*e.g.* expression is restricted to diseased tissues)	No point if conflicting evidence; Predicted damaging alterations in expression-specific tissues have a high predictive predictability (Zaidi, 2013)
		C-B4	Gene disruption experiment produces phenotype supportive of the proposed gene-disease relationship and phenotype can be rescued by addition of wildtype gene product	No point if conflicting evidence
		C-B5	Other strong data to support relevance of the gene with the proposed gene-disease relationship	
	C 4 needed*	C-C1	Gene function and/or expression profile is consistent with the phenotype (*e.g.* expression is not restricted to the diseased tissue)	No point if conflicting evidence
		C-C2	*in vivo* model organism (any genotype) produces phenotype supportive of the proposed gene-disease relationship	No point if conflicting evidence; Only applies if C-B2 is not met
		C-C3	Gene disruption experiment produces phenotype supportive of the proposed gene-disease relationship	No point if conflicting evidence; Only applies if C-B4 is not met
		C-C4	Gene located within a microdeletion/duplication syndrome described in multiple patients with consistent features with the evaluated phenotype	No point if conflicting evidence; AD, XL only; Reported microdeletions must be known to be of high penetrance; Only applies if C-A1 is not met
		C-C5	Gene product is in the same family, co-localizes, or physically interacts with the products of genes implicated in diseases with overlapping features	No point if conflicting evidence; Only applies if C-B1 is not met
		C-C6	Other data to support relevance of the gene with the evaluated phenotype	
		C-1	1 of B and 3 of C	
Suspected Candidate		S-1	Meets Candidate Criteria but the alteration(s) is/are classified as VUS according to Ambry Variant Classification (LaDuca, 2014)	
		S-2	Meets Candidate Criteria but phenotypic overlap is uncertain	
		S-3	At least VLP and 1 of B and 2 of C	
		S-4	At least VLP and 3 of C	For inherited compound heterozygous alterations, at least one must be at least VLP
Insufficient Evidence	D 1 Needed	I-D1	Does not meet Candidate, Suspected Candidate, or Non-Reported criteria	
		I-D2	Alteration(s) do/does not affect either the major isoform or the isoform which is abundantly expressed in the affected organs	
		I-D3	Alteration is not protein-truncating, splice,-disrupting or a missense change at a highly conserved amino acid	Mutant amino acid not seen in vertebrates during evolution
		I-D4	Proposed dominant inheritance (at the alteration level): Alteration is observed in healthy individuals	Excluding diseases known to demonstrate age-related and/or reduced penetrance
		I-D5	Proposed LOF mechanism among single, heterozygous truncating mutations: Healthy population databases indicate that haploinsufficiency is tolerated	LOF alteration seen in healthy controls must be in the same isoform as candidate, not observed in close proximity to 3' terminus, and at a high confidence locus in terms of metrics; Excluding diseases known to demonstrate age-related and/or reduced penetrance
		I-D6	Proposed LOF mechanism (at the gene level): Available data suggest functional redundancy of the candidate gene	Functional redundancy according to MacArthur, 2012, Exome Aggregation Consortium, 2015
Non-Reported	F 1 Needed		Alteration does not co-segregate with disease in family	
			Alteration(s) not present in >30% of reads in proband	
			Proposed recessive inheritance: Homozygous or compound heterozygous candidate alteration is observed as homozygous in healthy population databases	LOF alteration seen in healthy controls must be in the same isoform as candidate, not observed in close proximity to 3' terminus, and at a high confidence locus in terms of metrics
			Single, heterozygous alteration with MAF >0.1%	
			Homozygous or compound heterozygous alterations with MAF >0.2%	

LaDuca H, *et al.* Genet Med. 2014. 16(11):830-7.
MacArthur DG, *et al.* Nature. 2014. 508:469-76.
MacArthur DG, *et al.* Science. 2012. 335(6070):823-8.
Reed DR, *et al.* BMC Genet. 2008. 9:4.
Zaidi S, *et al.* Nature. 2013. 44:220-3.
Exome Aggregation Consotrium (2015) doi: http://dx.doi.org/10.1101/030338

*To reach the evidence criteria level of "Candidate," the following points are needed: 1 of A or 2 of B or 4 of C or 1 of B and 3 of C.