Guidelines for actionable variants

Gene	*Type of mutation*	*Justification*	*Reference*
GCK	**Immediately actionable**		
	All stop mutations	Loss of function	(1)
	All frame-shift mutations	Loss of function	(1)
	All exon deletions except for deletion of Exon 1A	Loss of function	(1)
	Duplication of exon 2 and 3	Previously seen to co-segregate with MODY in Danish patients	Unpublished
	Whole gene deletion	No gene	(2)
	Missense mutations: • Gly72Arg • Ala176Thr • Arg191Trp • Arg191Gln • Thr206Met • Thr228Met • Ala456Val	Pathogenic variants	Appendix 1
	Splice mutations: • c.45+1G>T (PMID: 15928245) • c.483+1G>A • c.864-1G>A	Pathogenic variants	Appendix 1
	Possibly actionable variants		
	All in-frame insertions, deletion or duplications	Possible loss of function	(1)
	Splice mutations 3 nucleotides into the intron region.	Likely to cause alternative splicing	(1)
	Missense mutations	Likely to be pathogenic	(3)
	Promoter: Islet promoter variant in c.-71G>C	Reduces gene expression in vitro through loss of regulation by Sp1	(1,4)
	Exon deletions of exon 1A	Possible loss of function	(1)
	Non-actionable variants		
	Common missense with a MAF of more than 0.5% in the Gnomad database or in 6,293 of Danish population-based of unselected samples.	Variants of no clinical relevance	(1)
	• Thr343Pro • Thr343Arg	Variants of no clinical relevance	(5) Appendix 2
	Mutations located more than 3 nucleotides into the intron region	Variants of no clinical relevance	(1)
	Synonymous mutations	Variants of no clinical relevance	(1)

Gene	*Type of mutation*	*Justification*	*Reference*
HNF1A	**Immediately actionable**		
	All stop mutations	Loss of function	(6)
	All frame-shift mutations	Loss of function	(6)
	All exon deletions	Loss of function	(6)
	Whole gene deletion	No gene	(6)
	Missense mutations: • Arg131Trp • Arg159Gln • Arg159Trp • Arg203Cys • Arg203His • Arg229Pro • Cys241Gly • Thr260Met • Arg263His • Arg271Gln • Arg271Trp • Val370Phe • Pro379Ala • Pro447Leu	Pathogenic variants	Appendix 1
	Possibly actionable variants		
	All in-frame insertions, deletion or duplications	Possible loss of function	(6,7)
	Splice mutations 3 nucleotides into the intron region.	Likely to cause alternative splicing	(6)
	Missense variants	Likely to be pathogenic	(6,8)
	Splice mutations: c.1502-6G>A	Loss of function as it leads to skipping of exon 7 and has been found in 15 previous families.	(6,9,10)
	Variants requiring no actions		
	Common missense with a MAF of more than 0.5% in the Gnomad database or in 6293 of Danish population-based of unselected samples.	Variants of no clinical relevance	(6)
	Mutations located more than 3 nucleotides into the intron region	Variants of no clinical relevance	(6)
	Synonymous mutations	Variants of no clinical relevance	(6)

Gene	*Type of mutation*	*Justification*	*Reference*
HNF4A	**Immediately actionable**		
	All stop mutations in exon 1-7	Loss of function	(6)
	All frame-shift mutations in all exons?	Loss of function	(6)
	All exon deletions	Loss of function	(6)
	P2 promoter: • C.-181G>A • C.-178 A/G	Affecting transcription factor binding sites	(11) Appendix 1
	Whole gene deletion	No gene	(12)
	Missense mutations: • Arg63Trp • Arg112Trp • Arg114Trp • Arg290Ser • Arg309Cys	Pathogenic variants	Appendix 1
	Possibly actionable variants		
	All in-frame insertions, deletion or duplications	Possible loss of function	(6)
	Splice mutations 3 nucleotides into the intron region.	Likely to cause alternative splicing	(6)
	c.319+5G>A Hg19: 43036120G>A Hg38: 44407480G>A	Causing aberrant splicing	(13) (https://databases.lovd.nl/shared/genes/HNF4A)
	Missense mutations	Likely to be pathogenic	(6)
	Exon duplication	Possible loss of function	NA
	P2-Promoter Any mutations located within this region: Hg19: Chr20: 42984246-42984321 Hg38: Chr20: 44355606-44355681		(14-16) Total P2: https://www.ncbi.nlm.nih.gov/nuccore/AF509467.1
	Variants not actionable		
	Common missense with a MAF of more than 0.5% in the Gnomad database or in 6293 of Danish population-based of unselected samples.	Variants of no clinical relevance	(6)
	• Val380Ile	Variant of no clinical relevance	Appendix 2
	Mutations located more than 3 nucleotides into the intron region	Variants of no clinical relevance	(6)
	Synonymous mutations	Variants of no clinical relevance	(6)

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