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Variant: NM_000536.4(RAG2):c.829dup (p.Tyr277fs)

Version: 1.0

CA1964194540

1075544 (ClinVar)

Gene: RAG2 (HGNC:5897)
Condition: recombinase activating gene 2 deficiency (MONDO:0000573)
Inheritance Mode: Autosomal recessive inheritance
UUID: c89cc531-8b5f-4912-b847-d76d082aaf68
Approved on: 2024/1/17
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HGVS expressions

NM_000536.4(RAG2):c.829dup (p.Tyr277fs)
NM_000536.4:c.829dup
NC_000011.10:g.36593340dup
CM000673.2:g.36593340dup
NC_000011.9:g.36614890dup
CM000673.1:g.36614890dup
NC_000011.8:g.36571466dup
NG_007573.1:g.9897dup
NG_033154.1:g.3848dup
ENST00000527033.6:c.829dup
ENST00000529083.2:c.829dup
ENST00000532616.2:c.829dup
ENST00000311485.8:c.829dup
ENST00000311485.7:c.829dup
ENST00000524423.1:n.131+4762dup
ENST00000618712.4:c.829dup
NM_000536.3:c.829dup
NM_001243785.1:c.829dup
NM_001243786.1:c.829dup
NM_001243785.2:c.829dup
NM_001243786.2:c.829dup

Pathogenic

Met criteria codes 4

PM2_Supporting PVS1 PP4 PS3_Moderate

Not Met criteria codes 2

PM1 PM3

Evidence Links 0

Expert Panel

Severe Combined Immunodeficiency Disease VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RAG2 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The NM_000536.4:c.829dup variant in RAG2 is a frameshift variant predicted to result in a truncated protein (p.Tyr277Leufs*4). Although this variant is expected to escape nonsense-mediated decay (NMD), it would be expected to disrupt approximately 47% of the RAG2 protein. In addition, this variant would be expected to disrupt/remove the entire PHD domain (amino acids 414-487), which is defined as a mutational hotspot/critical functional domain by the ClinGen SCID VCEP (PMID: 15964836). PVS1 met. This variant is absent in gnomAD, which is below the threshold for max filtering allele frequency for PM2_Supporting set by the ClinGen SCID VCEP for RAG2 (<0.0000588). In an experimental study, this variant demonstrates zero recombination activity, which is below the threshold outlined by the ClinGen SCID VCEP (< 25% wildtype activity) for PS3_Moderate (PMID: 31058115). This variant has been reported in three patients. One patient in a cohort of SCID patients (0.5p) with T-B-NK+ immunophenotype (0.5p) was identified with this variant along with a co-occurring RAG2 p.Phe183Asn variant, though phase was not reported (PMID: 24144642) (1p, PP4). A second patient with a later onset CID-like phenotype was identified with this variant along with a co-occurring RAG2 p.Glu170Gly variant (only one parent tested and was heterozygous for the variant) (PMID: 31058115). The p.Phe183Asn and p.Glu170Gly variants have not yet been classified by the ClinGen SCID VCEP. A third patient with Omenn syndrome was identified with this variant; however, the variant was heterozygous, and a second variant in RAG2 was not identified (PMID: 34851571). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive SCID based on the ACMG criteria applied: PVS1, PM2_Supporting, PS3_Moderate, and PP4 as specified by the ClinGen SCID VCEP (VCEP specifications version 1).

Met criteria codes

PM2_Supporting	✔	Variant is absent in gnomAD
PVS1	✔	The c.829dup variant is a frameshift variant (p.Tyr277Leufs*4) with an expected premature termination codon at p.279. The total number of amino acids is 528, so although this variant would be expected to escape NMD (RAG2 has only a single coding exon), approximately 47% of the total protein would be deleted. In addition, this variant would be expected to delete the entire PHD domain (amino acids 414-487), which is a critical region for protein function (PMID: 15964836). PVS1 met.
PP4	✔	I have counted the SCID patient in PMID: 24144642 as meeting PP4 though it may be a bit of a stretch: Everyone in cohort seems to have T-B-NK+ SCID and everyone had severe enough disease to undergo HSCT (so I am presuming diagnostic criteria for SCID was met even though this was not explicitly stated in the paper): 0.5p +0.5p = 1p = PP4 met with no modification. Other patients reported do not meet PP4. PMID: 34851571 has diagnosis of Omenn syndrome but only single heterozygous RAG variant reported (no second variant identified). PMID: 31058115 has later onset disease but does not meet SCID or leaky SCID criteria, phenotype more consistent with later onset CID.
PS3_Moderate	✔	Recombinase activity of this variant is zero (PMID: 31058115), which meets ClinGen SCID VCEP's criteria for PS3_moderate (< 25% wildtype activity).

Not Met criteria codes

PM1	✖	only for missense variants
PM3	✖	Variant co-occurs with p.Phe183Asn (phase unknown) in SCID patient PA30 (PMID: 24144642). Variant co-occurs with p.E170G (likely trans but only mother tested so phase not completely confirmed) in patient with later onset CID phenotype (PMID: 31058115). Neither p.Phe183Asn nor p.E170G have yet been curated by ClinGen SCID VCEP. Since

phase not confirmed, even if both variants turn out to be P, the max awarded would be 0.5p per proband (1p), so it's possible that PM3 could be applied at regular strength (no modification) in future but that's only IF both co-occurring variants turned out to be fully pathogenic.

Curation History

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