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Effect of splice-site mutations in X-linked chronic granulomatous disease

Dear Sir,

We agree with the caution expressed by Dr. Roesler in his letter to the editor concerning the transcriptional and translational effect of the disease-causing splice mutation we report in a carrier of X-linked chronic granulomatous disease (CGD) (1). The lack of protein expression we observed in >90% of the patient's neutrophils could be due to production of a truncated protein because of the introduced stop codon, an unstable protein due to skipping of exon 4, or some other problem with transcription and translation of the mutant DNA/RNA. Analysis of the mRNA transcripts produced from the cDNA containing the mutation would be necessary to determine the exact effect. We were careful in our article to state that the mutation "predicted" the introduction of a stop codon resulting in a truncated protein. A previously reported mutation in the same intron at -8 from the normal 3' splice site also introduced an early splice site and did lead to termination of the transcript in exon 4 (2). The alternate interpretation of exon skipping offered by Dr. Roesler is certainly feasible, but the end result – no protein expression in the affected population of cells, causing CGD – is the same.

The clinical course of the carrier patient described by Dr. Roesler is also interesting and is similar to the patient in our report. Our patient is also doing well, with no serious infections since her diagnosis and the initiation of prophylactic treatment in 2004. She has since had a baby (female), with no complications. We will soon test the baby for carrier status, but, so far, the baby is quite healthy.

Thank you for the opportunity to reply to Dr. Roesler's letter and we appreciate his comments.

Sincerely,

Linda C. McPhail, PhD (for the authors)

Reference List

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2. Rae J, Newburger PE, Dinanuer MC, Noack D, Hopkins PJ, Kuruto R, Curnutte JT. X-Linked chronic granulomatous disease: mutations in the CYBB gene encoding the gp91-phox component of respiratory-burst oxidase. *Am J Hum Genet* 1998 Jun;62(6):1320–31. [PubMed: 9585602]