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TITLE: Data double take: three examples of atypical pathogenic alterations detected in exome sequencing data

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Clinical exome sequencing has become a routinely ordered test, especially for pediatric patients with phenotypes that are difficult to assign to specific genetic etiologies. Variant calling algorithms typically identify single nucleotide variants (SNVs) and small insertions/deletions (indels) with accuracy and ease. Because exome data can contain information about more complex alterations such as micro translocations and duplications too small to be detected by micro array, additional steps can be taken to ensure that such alterations are not excluded from analysis. We present three cases in which atypical damaging alterations were identified by analyzing exome data beyond the typical SNVs and small indels. The first case was a 17y old male with bilateral pigmentary maculopathy, cone-rod dystrophy, poor vision, and other signs of severe retinal dystrophy. A single paternally inherited nonsense alteration was identified using our exome analysis pipeline. Haploinsufficiency of *CRB1* is not typically pathogenic. To determine if a second pathogenic alteration was present in *CRB1*, exome sequencing data was analyzed by a fusion detection pipeline, and a second maternally inherited micro duplication disrupting exon 2 was detected. In a second unrelated case, a 14y old male presented with frequent infections, high IgE, and CD4 lymphopenia. A paternally inherited 7bp insertion was identified in the proband in *DOCK8*, a gene associated with autosomal recessive hyper-IgE recurrent infection syndrome (Job syndrome). Again, analysis by our fusion pipeline exposed a maternally inherited translocation between chromosome 3 and intron 2 of *DOCK8*, resulting in loss of exons 1-2 of *DOCK8*. Interestingly, there are several literature reports describing deletion of exon 1-2 of *DOCK8*, suggesting that the translocation may represent a recurrent and relatively common cause of Dock8 deficiency. Finally, a 5y old female presented with elevated creatinine kinase, exercise-related muscle fatigue and pain, and muscle biopsy with decreased calpain3 staining. No definitive alterations were identified until coverage statistics were analyzed, which revealed a homozygous deletion encompassing *CAPN3* and part of *GANC*, confirming the diagnosis of LGMD2A. These results demonstrate that in some cases, exome data contains information beyond SNVs and small indels. Thorough analysis of the data can lead to identification of atypical, but nevertheless important disease causing alterations.