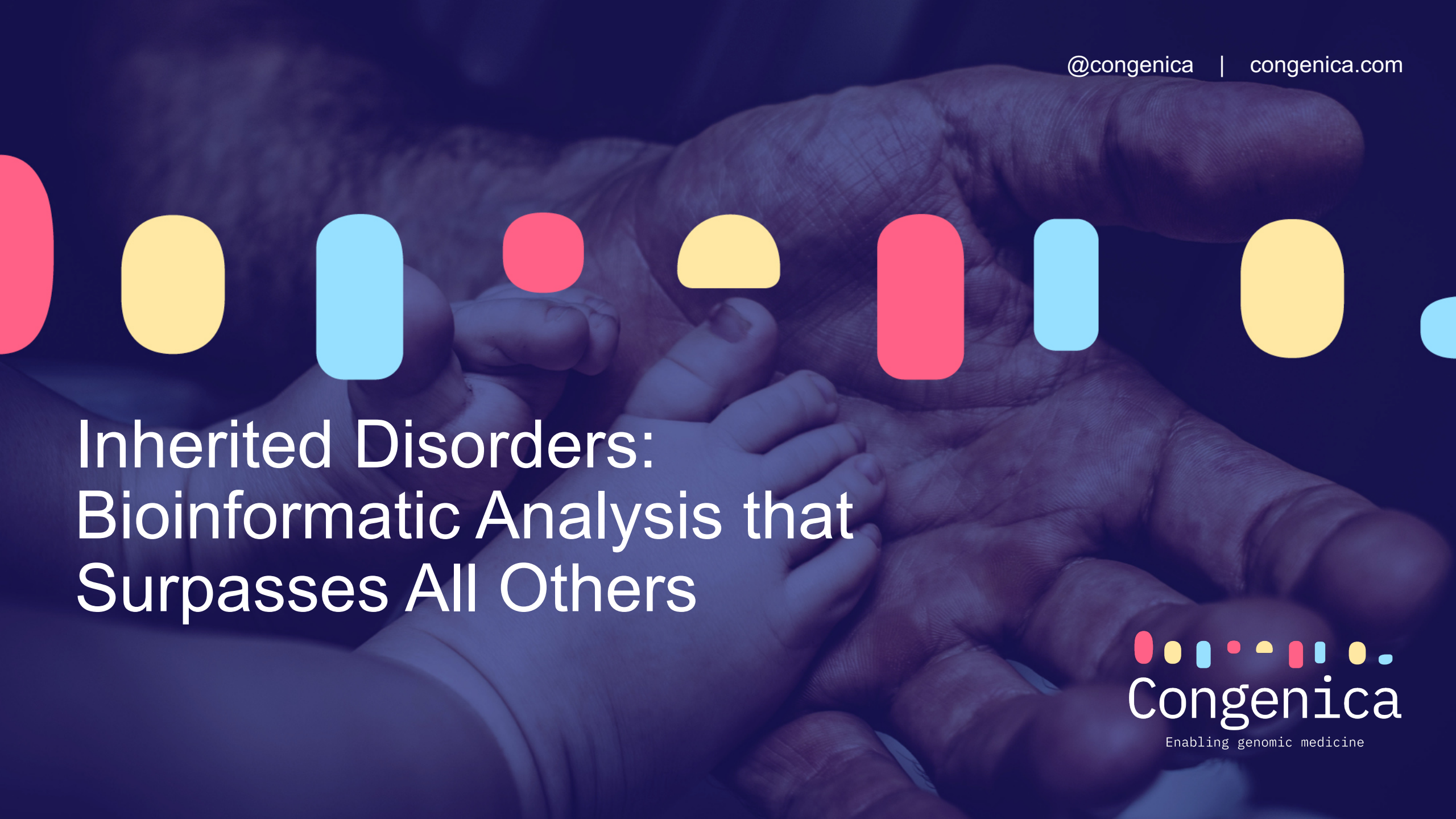

Inherited Disorders: Bioinformatic Analysis that Surpasses All Others

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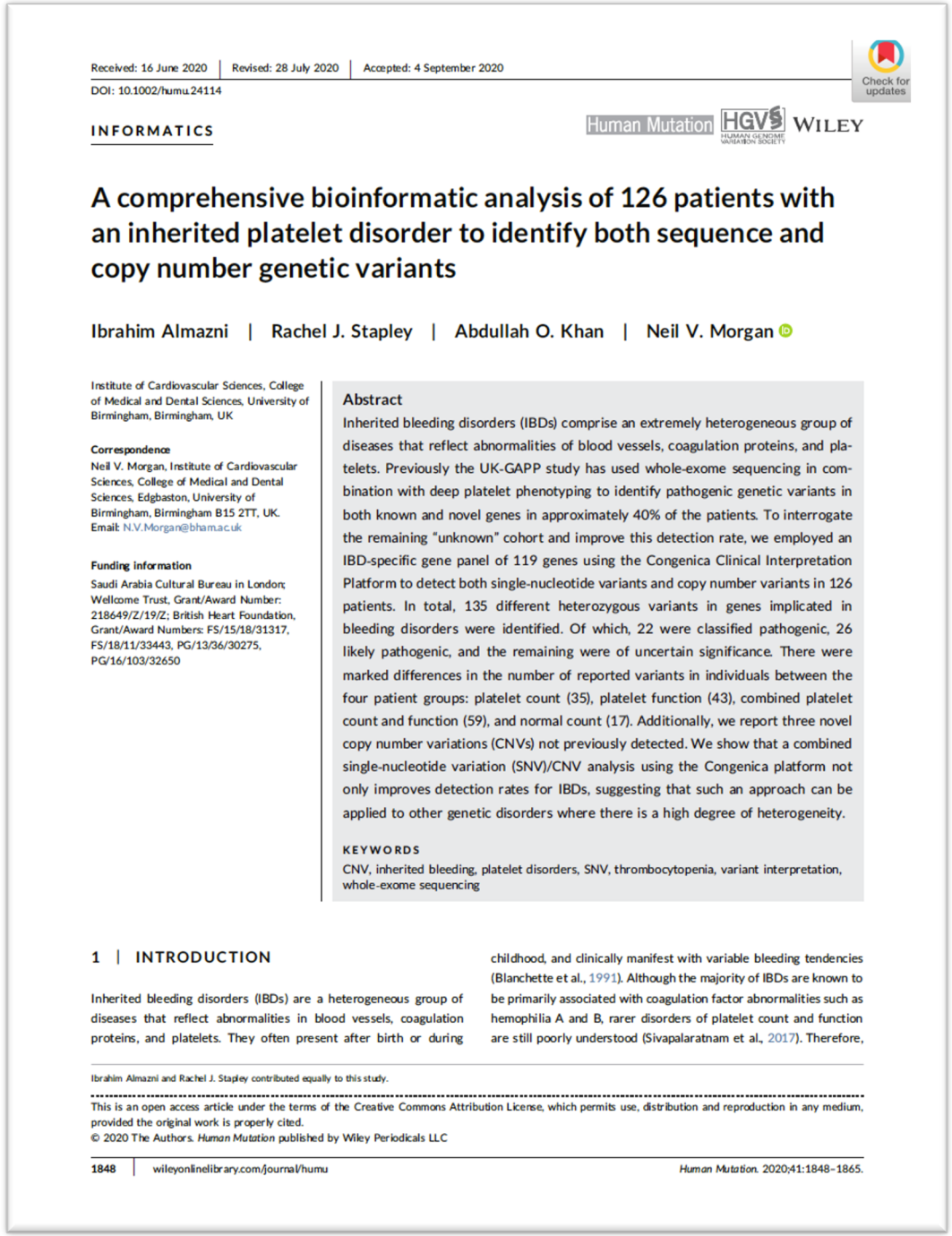
Congenica enhances the detection of inherited platelet disorders

A recent study from the University of Birmingham has shown that the Congenica platform demonstrated superior performance in identifying the genetic causes of platelet-related bleeding disorders.

"*Congenica's highly sensitive software can be used for detecting SNVs and CNVs in whole exome sequencing data. We see this as* ***a significant leap forward*** *in the ability to classify hugely complex disorders with a high degree of heterogeneity within the wider scientific community and the potential for providing* ***concise and definitive diagnosis for patients***."

Dr Neil Morgan, University of Birmingham



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INFORMATICS

Human Mutation HGVS WILEY

A comprehensive bioinformatic analysis of 126 patients with an inherited platelet disorder to identify both sequence and copy number genetic variants

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Abstract

Inherited bleeding disorders (IBDs) comprise an extremely heterogeneous group of diseases that reflect abnormalities of blood vessels, coagulation proteins, and platelets. Previously the UK-GAPP study has used whole-exome sequencing in combination with deep platelet phenotyping to identify pathogenic genetic variants in both known and novel genes in approximately 40% of the patients. To interrogate the remaining "unknown" cohort and improve this detection rate, we employed an IBD-specific gene panel of 119 genes using the Congenica Clinical Interpretation Platform to detect both single-nucleotide variants and copy number variants in 126 patients. In total, 135 different heterozygous variants in genes implicated in bleeding disorders were identified. Of which, 22 were classified pathogenic, 26 likely pathogenic, and the remaining were of uncertain significance. There were marked differences in the number of reported variants in individuals between the four patient groups: platelet count (35), platelet function (43), combined platelet count and function (59), and normal count (17). Additionally, we report three novel copy number variations (CNVs) not previously detected. We show that a combined single-nucleotide variation (SNV)/CNV analysis using the Congenica platform not only improves detection rates for IBDs, suggesting that such an approach can be applied to other genetic disorders where there is a high degree of heterogeneity.

KEYWORDS
CNV, inherited bleeding, platelet disorders, SNV, thrombocytopenia, variant interpretation, whole-exome sequencing

1 | INTRODUCTION

Inherited bleeding disorders (IBDs) are a heterogeneous group of diseases that reflect abnormalities in blood vessels, coagulation proteins, and platelets. They often present after birth or during childhood, and clinically manifest with variable bleeding tendencies (Blanchette et al., 1991). Although the majority of IBDs are known to be primarily associated with coagulation factor abnormalities such as hemophilia A and B, rarer disorders of platelet count and function are still poorly understood (Sivapalaratnam et al., 2017). Therefore,

Ibrahim Almazni and Rachel J. Stapley contributed equally to this study.

WES Analysis achieves 96% increase in classified variants

An Inherited Bleeding Disorder specific gene panel of 119 genes was used to detect both single nucleotide variants and copy number variants.

- 135 different heterozygous variants identified:
- 22 classified pathogenic
- 26 likely pathogenic

Congenica showed a superior performance when compared with other bioinformatics platforms

- 25 variants were identified by Congenica as well as other bioinformatic tools
- A further 24 variants were classified by the Congenica bioinformatics platform

Access the paper:

https://doi.org/10.1002/humu.24114

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