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Decoding telomere gene variation through saturation genome editing: from functional genomics to clinical interpretation

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Decoding Telomere Gene Variation through Saturation Genome Editing: From Functional Genomics to Clinical Interpretation

1. Large-scale genomic sequencing is transforming diagnostic and decision-making practices in modern medicine, shifting the main challenge in clinical genomics from detecting variants to interpreting their clinical relevance.
2. Unequal representation in genomic reference datasets increases the burden of variants of uncertain significance and contributes to inequities in clinical decision-making.
3. Reliable clinical variant classification requires functional evidence, in addition to computational prediction, particularly for variants with uncertain or intermediate effects.
4. Multiplexed assays of variant effect (MAVEs) strengthen clinical variant interpretation by providing scalable functional evidence for clinically relevant genes.
5. Degenerative telomere biology disorders and telomere-associated cancer predisposition both arise from disruption of the balance between telomere protection, replication, and elongation.
6. Partial disruption of shelterin components such as POT1 and TIN2 can give rise to divergent telomere phenotypes, depending on telomerase activity, residual end protection, and tissue-specific replicative demands.
7. Quantitative differences in functional impairment can explain variation in cancer risk more accurately than binary variant classification alone (Chapter 4 of this thesis).
8. Although pathogenic *POT1* variants are rare in melanoma, they can be clinically meaningful in well-defined high-risk families when supported by functional validation. (Chapters 6 & 7 of this thesis).
9. In *TINF2*-associated cancer predisposition, melanoma and non-medullary thyroid carcinoma are most consistently associated with indications for genetic testing and surveillance, while additional tumour types may be relevant in families with suggestive segregation patterns (Chapter 5 of this thesis).
10. High-throughput functional data can be incorporated into ACMG/AMP and ClinGen variant classification frameworks when quantitatively calibrated against appropriate truthsets (Chapters 4 & 8 of this thesis).
11. High-throughput functional assays most effectively inform clinical risk stratification and management when supported by standardised data sharing and interpreted within an appropriate clinical and familial context.
12. Goethe's observation that "*in nature we never see anything isolated, but everything in connection with something else which is before it, beside it, under it and over it*" remains highly relevant to clinical genetics, where the interpretation of genetic variation depends on biological, familial, and population context (Johann Wolfgang von Goethe (1825)).