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The benefits of exploiting rare genetic disorders to better understand human health and disease

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If a genetic disease affects less than 5 in 10,000 people, it is categorised as a rare or orphan disease. This branding to a 'rare' or 'orphan' status is misleading in some regards. Due to the stigma of being 'rare', research funders often consider them to be of a lesser priority. You can of course understand their pragmatic view point: 'only a small percentage of people will benefit from research on rare diseases; therefore they will have less overall impact'. Consequently, funding opportunities become restrictive and research progress is slow. This lack of forward research momentum has hampered our understanding of many rare genetic disorders. It is estimated that one in 25 children is affected with a genetic disorder. So, if you consider them as a collective, they are not so rare. Thankfully, perception of rare diseases has changed dramatically, mainly due to the perseverance of rare disease charities and families affected by these disorders. In fact, the research landscape of rare diseases is now in a much better place. This review series highlights the unique opportunity that these diseases present. Patients with rare diseases become in essence a human genetic model, which allows for very detailed research into new signalling mechanisms linked to human health and disease.

Some genetic disorders are apparent at birth while others are typically diagnosed early in childhood. The cover page of this review series illustrates a cartoon of a child with a rare genetic disorder being led by her parent. The cover page has a rough sketch of a signalling pathway that has been delineated through research on several rare genetic disorders, of which will be further discussed in this review series. The child's representation of therapy towards a tumour is indicative of the current success story on Tuberous Sclerosis Complex (TSC). Through working closely with patient families with TSC, research breakthroughs were made that revealed the molecular mechanism behind their tumour predisposition. Our understanding of TSC and mammalian target of rapamycin (mTOR) will be further discussed by Dodd & Dunlop [1]. As well as being predisposed to tumours, neurological complications are also associated with TSC, which will be discussed in the review by Tee *et al.* [2].

The signalling pathway upstream of TSC and mTOR is represented in the cover page and is closely associated with other tumour predisposition genetic diseases. Cowden's disease, where the *LKB1* gene is mutated is reviewed in depth by Shorning & Clarke [3]. They highlight the importance of studying genetic models and then discuss how they have increased our fundamental understanding of mechanisms linked to tumour biology. At the top of the depicted signalling pathway, Leslie & Longy [4] describe Peutz-Jeghers syndrome, which is caused by mutations in *PTEN*, a lipid phosphatase that directly opposes the insulin stimulated phosphoinositide 3-kinase signalling pathway. Rad & Tee [5] then discuss neurofibromatosis, where patients have mutations in

neurofibromin. While neurofibromin is well characterised for its ability to repress cell proliferation through inhibition of the Ras small G protein, neurofibromin has many other interesting tumour suppressor functions that are closely linked to malignancy. Another closely related tumour predisposition syndrome is Birt-Hogg-Dubé (BHD). The molecular mechanism behind why BHD patients are at increased risk of spontaneous pneumothorax is currently unclear. The review by Kennedy *et al.* describes the lung pathology related to BHD and a stretch hypothesis leading to the formation of cysts and then lung collapse [6].

The review on alkaptonuria (also known as black bone disease) is described by Gallagher *et al.* [7], where these patients are unable to process phenylalanine and tyrosine leading to acid accumulation in their bones and tissue. Research breakthroughs of alkaptonuria have contributed to our 'fundamental' understanding of the pathogenesis of osteoarthritis, which mostly affects the aging population. Here in this review, they also eloquently describe the history of iconic medical researchers who valued rare diseases in the study of biomedical sciences.

In the review entitled 'Making the invisible visible' Prof. Maurice van Steensel then describes how genetic skin diseases allows for the study of human biology on the canvas of the skin [8]. Through genetic analysis and research of skin disorders much progress has been made in our basic understanding of skin pigmentation, a topic covered in this review.

I hope you enjoy this review series on several prominent genetic disorders. While research in these research topics will undoubtedly led to advances in health care, there are many more disorders that are in desperate need for curious minds and research funding. By researching new mechanisms of pathology in rare genetic disorders, we enhance our overall understanding of more common disorders or diseases within the general population.

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