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Abstract Topic: - Evolutionary and population genetics

Abstract Title: - Vertebrate α1-proteinase inhibitors - Origin, Evolution, and Pathophysiological Diversifications

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Aims: - To study the detailed evolutionary origin of α1-proteinase inhibitors focusing on details of functional overlaps and pathophysiological details of these proteinase inhibitors.

Methods: - Using comparative genomics and bioinformatics analyses of α1-proteinase inhibitors aided by ENSEMBL Genome browsers, homology detection tools and MEGA-X.

Results: - We found that this locus duplicated and became two loci one harboured non-inhibitory AGT, and the other locus expanded by tandem duplications and expanded substantially from single serpin (in lampreys) to three (in elephant shark), five (in Fugu), seven (in birds and frogs) and 11 serpins (in human). This ancestral locus harbours the α1-antitrypsin-like gene, which performs heparin-binding angiotensinogen (AGT/SERPINA8). This AGT protein harbours RCL, which remained from inhibitory (GTEAKAETVVGIMPI†SMPPT) in three different lampreys, Lethenteron, Lampetra, and Petromyzon to non-inhibitory in various vertebrates like tilapia (GAEPQDPTQEEGVPL†KLSIN), flycatcher (GTDQPADPAAQKEDG†VYLDV), turtle (GAEELLEENGDSLPL†EIQLN) and human (EREPTESTQQLNKPE†VLEVT) over 500 MY. We further created three distinct sub-groups within vertebrate group V2 serpins as

(a) Sub-group V2_I is primarily α1-antitrypsin-like genes, arose by tandem duplications and functional diversifications by rapid RCL mutations with α1-antitrypsin (SERPINA1), α1-antitrypsin-related protein(SERPINA2), antichymotrypsin(SERPINA3), kallistatin (SERPINA4), protein C inhibitor (PAI3/SERPINA5), corticosteroid-binding globulin (SERPINA6), thyroxine-binding globulin (SERPINA7), centerin (SERPINA9), protein Z-dependent proteinase inhibitor (ZPI/SERPINA10), Vaspin (SERPINA12) and two functionally uncharacterized serpins (SERPINA11 and SERPINA13).

(b) Sub-group V2_II harbors AGT, which is the primary carrier of active angiotensin hormones of the renin-angiotensin system that regulates body fluid homeostasis, blood pressure, and blood vessel formation.

(c) Sub-group V2_III possesses heparin factor II (HCII) which serves thrombin inhibitory in the presence of certain glycosaminoglycans and HCII is conserved in vertebrates as embedded inside the largest intron of the PIK4CA gene.

Conclusions: - We found that the ancestral α1-proteinase inhibitor locus is conserved from lampreys to humans and it is older than 500 million years (MY). This hinted that the angiotensin system and the blood coagulation system overlapped and diverged during vertebrate evolution.

Keywords: - We found that this locus duplicated and became two loci one harboured non-inhibitory AGT, and the other locus expanded by tandem duplications and expanded substantially from single serpin (in lampreys) to three (in elephant shark), five (in Fugu), seven (in birds and frogs) and 11 serpins (in human). This ancestral locus harbours the α1-antitrypsin-like gene, which performs heparin-binding angiotensinogen (AGT/SERPINA8). This AGT protein harbours RCL, which remained from inhibitory (GTEAKAETVVGIMPI†SMPPT) in three different lampreys, Lethenteron, Lampetra, and Petromyzon to non-inhibitory in various vertebrates like tilapia (GAEPQDPTQEEGVPL†KLSIN), flycatcher (GTDQPADPAAQKEDG†VYLDV), turtle (GAEELLEENGDSLPL†EIQLN) and human (EREPTESTQQLNKPE†VLEVT) over 500 MY. We further created three distinct sub-groups within vertebrate group V2 serpins as

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