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Avian Influenza Virus Hemagglutinins H2, H4 and H8 support a highly pathogenic phenotype

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Naturally occurring highly pathogenic avian influenza viruses (HPAIV) specify hemagglutinins (HA) with a polybasic cleavage site (HA) only of serotypes H5 and H7. To elucidate the ability of other HA subtypes to support a highly pathogenic phenotype, we cloned HA genes of the serotypes H1, H2, H3, H4, H6, H8, H9, H10, H12 and H15, introduced the polybasic cleavage site from A/Chicken/Italy/8/98 (H5N2) and rescued reassortants by co-transfection with the other seven genome segments of the LPAIV A/Chicken/Emirates/R66/2002 (H9N2) or HPAIV A/Swan/Ruegen/R65/2006 (H5N1), a clade 2.2 strain. Oculonasal infection of chickens with these reassortants displayed varying pathogenicity. Recombinants carrying engineered H2, H4 and H8 in the HPAIV background induced lethal disease in chicken similar to 'classical' HPAIV. To assess the virulence more precisely, we determined the intravenous pathogenicity indices (IVPI). With IVPIs of 2.79, 2.37, and 2.85, the H2, H4, and H8 reassortants fulfill the criterion of a 'classical' H5 or H7 HPAIV; the homologous H5N1 A/Swan/Ruegen/R65/2006 has an IVPI of 2.88. These results demonstrate that also non H5/H7 HA with a polybasic cleavage site can support a highly pathogenic phenotype. Therefore, natural evolution to HPAIV from low-pathogenic precursors may be confined to H5 and H7 just because of their unique predisposition for acquisition of a polybasic HA cleavage site mutation.